

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number  
**WO 03/106648 A2**

- (51) International Patent Classification<sup>7</sup>: C12N    (74) Agents: LICATA, Jane, Massey et al.; Licata & Tyrell P.C., 66 E. Main Street, Marlton, NJ 08053 (US).
- (21) International Application Number: PCT/US03/18934    (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 16 June 2003 (16.06.2003)    (25) Filing Language: English    (26) Publication Language: English
- (30) Priority Data: 60/389,327    14 June 2002 (14.06.2002) US    (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (for all designated States except US): DI-ADEXUS, INC. [US/US]; 343 Oyster Point Boulevard, San Francisco, CA 94080 (US).
- (72) Inventors; and    (75) Inventors/Applicants (for US only): SALCEDA, Susana [AR/US]; 4118 Cresendo Avenue, San Jose, CA 95136 (US). MACINA, Roberto, A. [AR/US]; 4118 Crescendo Avenue, San Jose, CA 95136 (US). TURNER, Leah, R. [US/US]; 939 Rosette Court, Sunnyvale, CA 94086 (US). SUN, Yongming [CN/US]; 551 Shoal Drive, Redwood City, CA 94065 (US). LIU, Chenghua [CN/US]; 1125 Ranchero Way #14, San Jose, CA 95117 (US).

Published:

without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/106648 A2

(54) Title: COMPOSITIONS AND METHODS RELATING TO BREAST SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acid molecules and polypeptides present in normal and neoplastic breast cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions containing the nucleic acid molecules, polypeptides, antibodies, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast, identifying breast tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered breast tissue for treatment and research.

**THIS PAGE BLANK (USPTO)**

**COMPOSITIONS AND METHODS  
RELATING TO BREAST SPECIFIC GENES AND PROTEINS**

**FIELD OF THE INVENTION**

5       The present invention relates to newly identified nucleic acids and polypeptides present in normal and neoplastic breast tissue, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions comprising the 10 nucleic acids, polypeptides, antibodies, variants, derivatives, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast, identifying breast tissue, monitoring and modifying breast tissue development and differentiation, and identifying and/or designing agonists 15 and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered breast tissue for treatment and research.

**BACKGROUND OF THE INVENTION**

20       Excluding skin cancer, breast cancer, also called mammary tumor, is the most common cancer among women, accounting for a third of the cancers diagnosed in the United States. One in nine women will develop breast cancer in her lifetime and about 192,000 new cases of breast cancer are diagnosed annually with about 42,000 deaths. Bevers, *Primary Prevention of Breast Cancer*, in BREAST CANCER, 20-54 (Kelly K Hunt et al., ed., 2001); Kochanek et al., Nat'l. Vital Statistics Reports 49(1):14 (2001).

25       In the treatment of breast cancer, there is considerable emphasis on detection and risk assessment because early and accurate staging of breast cancer has a significant impact on survival. For example, breast cancer detected at an early stage (stage T0, discussed below) has a five-year survival rate of 92%. Conversely, if the cancer is not detected until a late stage (i.e., stage T4), the five-year survival rate is reduced to 13%. 30       AJCC Cancer Staging Handbook pp. 164-65 (Irvin D. Fleming et al. eds., 5<sup>th</sup> ed. 1998). Some detection techniques, such as mammography and biopsy, involve increased

discomfort, expense, and/or radiation, and are prescribed only to patients with an increased risk of breast cancer.

- Current methods for predicting or detecting risk of breast cancer are not optimal. One method for predicting the relative risk of breast cancer is by examining a patient's
- 5 risk factors and pursuing aggressive diagnostic and treatment regimens for high risk patients. A patient's risk of breast cancer has been positively associated with increasing age, nulliparity, family history of breast cancer, personal history of breast cancer, early menarche, late menopause, late age of first full term pregnancy, prior proliferative breast disease, irradiation of the breast at an early age and a personal history of malignancy.
- 10 Lifestyle factors such as fat consumption, alcohol consumption, education, and socioeconomic status have also been associated with an increased incidence of breast cancer although a direct cause and effect relationship has not been established. While these risk factors are statistically significant, their weak association with breast cancer limits their usefulness. Most women who develop breast cancer have none of the risk
- 15 factors listed above, other than increasing age. NIH Publication No. 00-1556 (2000).
- Current screening methods for detecting cancer, such as self-examination, ultrasound, and mammography have drawbacks that reduce their effectiveness or prevent their widespread adoption. Self-examination, while useful, is unreliable for the detection of breast cancer in the initial stages where the tumor is small and difficult to detect by
- 20 palpitation. Ultrasound measurements require skilled operators at an increased expense. Mammography, while sensitive, is subject to over diagnosis in the detection of lesions that have questionable malignant potential. There is also the fear of the radiation used in mammography because prior chest radiation is a factor associated with an increased incidence of breast cancer.
- 25 At this time, there are no adequate methods of breast cancer prevention. The current methods of breast cancer prevention involve prophylactic mastectomy (mastectomy performed before cancer diagnosis) and chemoprevention (chemotherapy before cancer diagnosis), which are drastic measures that limit their adoption even among women with, increased risk of breast cancer. Bevers, *supra*.
- 30 A number of genetic markers have been associated with breast cancer. Examples of these markers include carcinoembryonic antigen (CEA) (Mughal et al., JAMA 249:1881 (1983)) MUC-1 (Frische and Liu, J. Clin. Ligand 22:320 (2000)), HER-2/neu (Haris et al., Proc.Am.Soc.Clin.Oncology. 15:A96 (1996)), uPA, PAI-1, LPA, LPC, RAK

and BRCA (Esteva and Fritsche, *Serum and Tissue Markers for Breast Cancer*, in BREAST CANCER, 286-308 (2001)).

Breast cancers are diagnosed into the appropriate stage categories recognizing that different treatments are more effective for different stages of cancer. There are a variety of different schemes for staging breast cancer. One is known as the TNM staging system in which T stands for tumor size, N stands for node involvement and M stands for metastasis. Stage TX indicates that primary tumor cannot be assessed (i.e., tumor was removed or breast tissue was removed). Stage T0 is characterized by abnormalities such as hyperplasia but with no evidence of primary tumor. Stage Tis is characterized by carcinoma in situ, intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor. Stage T1 is characterized as having a tumor of 2 cm or less in the greatest dimension. Within stage T1, Tmic indicates microinvasion of 0.1 cm or less, T1a indicates a tumor of between 0.1 to 0.5 cm, T1b indicates a tumor of between 0.5 to 1 cm, and T1c indicates tumors of between 1 cm to 2 cm. Stage T2 is characterized by tumors from 2 cm to 5 cm in the greatest dimension. Tumors greater than 5 cm in size are classified as stage T3. A T4 stage tumor may be any size with an extension to either the chest wall or the skin. Within stage T4, T4a indicates extension of the tumor to the chest wall, T4b indicates edema or ulceration of the skin of the breast or satellite skin nodules confined to the same breast, T4c indicates a combination of T4a and T4b, and T4d indicates inflammatory carcinoma. AJCC Cancer Staging Handbook pp. 159-70 (Irvin D. Fleming et al. eds., 5<sup>th</sup> ed. 1998). In addition to standard staging, breast tumors may be classified according to their estrogen receptor and progesterone receptor protein status. Fisher et al., Breast Cancer Research and Treatment 7:147 (1986). Additional pathological status, such as HER2/neu status may also be useful. Thor et al., J.Nat'l.Cancer Inst. 90:1346 (1998); Paik et al., J.Nat'l.Cancer Inst. 90:1361 (1998); Hutchins et al., Proc.Am.Soc.Clin.Oncology 17:A2 (1998); and Simpson et al., J.Clin.Oncology 18:2059 (2000).

In addition to the staging of the primary tumor, breast cancer metastases to regional lymph nodes may be staged. Stage NX indicates that the lymph nodes cannot be assessed (e.g., previously removed). Stage N0 indicates no regional lymph node metastasis. Stage N1 indicates metastasis to movable ipsilateral axillary lymph nodes. Stage N2 indicates metastasis to ipsilateral axillary lymph nodes fixed to one another or to

other structures. Stage N3 indicates metastasis to ipsilateral internal mammary lymph nodes. Id.

Stage determination has potential prognostic value and provides criteria for designing optimal therapy. Simpson et al., J. Clin. Oncology 18:2059 (2000). Generally, pathological staging of breast cancer is preferable to clinical staging because the former gives a more accurate prognosis. However, clinical staging would be preferred if it were as accurate as pathological staging because it does not depend on an invasive procedure to obtain tissue for pathological evaluation. Staging of breast cancer would be improved by detecting new markers in cells, tissues, or bodily fluids that could differentiate between different stages of invasion. Progress in this field will allow more rapid and reliable methods for treating breast cancer patients.

Treatment of breast cancer is generally decided after an accurate staging of the primary tumor. Primary treatment options include breast conserving therapy (lumpectomy, breast irradiation, and surgical staging of the axilla), and modified radical mastectomy. Additional treatments include chemotherapy, regional irradiation, and, in extreme cases, terminating estrogen production by ovarian ablation.

Until recently, the customary treatment for all breast cancer was mastectomy. Fonseca et al., Annals of Internal Medicine 127:1013 (1997). However, recent data indicate that less radical procedures may be equally effective, in terms of survival, for early stage breast cancer. Fisher et al., J. of Clinical Oncology 16:441 (1998). The treatment options for a patient with early stage breast cancer (i.e., stage Tis) may be breast-sparing surgery followed by localized radiation therapy at the breast. Alternatively, mastectomy optionally coupled with radiation or breast reconstruction may be employed. These treatment methods are equally effective in the early stages of breast cancer.

Another staging scheme is Stage I, II, III and IV. In this scheme, Stage I is characterized as having a tumor of 2 cm or less and no lymph node involvement or metastasis. Stage II is characterized by a tumor of 2 cm to 5 cm and local or no lymph node involvement and no metastasis. Stage III is greater than 5 cm and local lymph node involvement and no metastasis. Stage IV is a metastatic tumor with no regard for size or lymph node involvement. Patients with Stage I and Stage II breast cancer require surgery with chemotherapy and/or hormonal therapy. Surgery is of limited use in Stage III and Stage IV patients. Thus, these patients are better candidates for chemotherapy and radiation therapy with surgery limited to biopsy to permit initial staging or subsequent

restaging because cancer is rarely curative at this stage of the disease. AJCC Cancer Staging Handbook 84, 164-65 (Irvin D. Fleming et al. eds., 5<sup>th</sup> ed. 1998).

To provide more treatment options to patients, efforts are underway to define an earlier stage of breast cancer with low recurrence that can be treated with lumpectomy without postoperative radiation treatment. While a number of attempts have been made to 5 classify early stage breast cancer, no consensus recommendation on postoperative radiation treatment has been obtained from these studies. Page et al., Cancer 75:1219 (1995); Fisher et al., Cancer 75:1223 (1995); Silverstein et al., Cancer 77:2267 (1996).

As discussed above, each of the methods for diagnosing and staging breast cancer 10 is limited by the technology employed. Accordingly, there is need for sensitive molecular and cellular markers for the detection of breast cancer. There is a need for molecular markers for the accurate staging, including clinical and pathological staging, of breast cancers to optimize treatment methods. Finally, there is a need for sensitive molecular and 15 cellular markers to monitor the progress of cancer treatments, including markers that can detect recurrence of breast cancers following remission.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill in the art from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. 20 Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

#### SUMMARY OF THE INVENTION

The present invention solves many needs in the art by providing nucleic acid 25 molecules, polypeptides and antibodies thereto, variants and derivatives of the nucleic acids and polypeptides, agonists and antagonists that may be used to identify, diagnose, monitor, stage, image and treat breast cancer and non-cancerous disease states in breast; identify and monitor breast tissue; and identify and design agonists and antagonists of 30 polypeptides of the invention. The invention also provides gene therapy, methods for producing transgenic animals and cells, and methods for producing engineered breast tissue for treatment and research.

One aspect of the present invention relates to nucleic acid molecules that are specific to breast cells, breast tissue and/or the breast organ. These breast specific nucleic acids (BSNAs) may be a naturally occurring cDNA, genomic DNA, RNA, or a fragment of one of these nucleic acids, or may be a non-naturally occurring nucleic acid molecule.

- 5 If the BSNA is genomic DNA, then the BSNA is a breast specific gene (BSG). If the BSNA is RNA, then it is a breast specific transcript encoded by a BSG. Due to alternative splicing and transcriptional modification one BSG may encode for multiple breast specific RNAs. In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that is specific to breast. More preferred is a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 95-156. In another preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-94. For the BSNA sequences listed herein, DEX0432\_001.nt.1 corresponds to SEQ ID NO: 1. For sequences with multiple splice variants, the parent sequence DEX0432\_001.nt.1, will be followed by DEX0432\_001.nt.2, etc. for each splice variant.
- 10 15 The sequences off the corresponding peptides are listed as DEX0432\_001\_aa.1, etc. For the mapping of all of the nucleotides and peptides, see the table in the Example 1 section below.

This aspect of the present invention also relates to nucleic acid molecules that selectively hybridize or exhibit substantial sequence similarity to nucleic acid molecules encoding a breast Specific Protein (BSP), or that selectively hybridize or exhibit substantial sequence similarity to a BSNA. In one embodiment of the present invention the nucleic acid molecule comprises an allelic variant of a nucleic acid molecule encoding a BSP, or an allelic variant of a BSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid sequence that encodes a BSP or a part of a nucleic acid sequence of a BSNA.

In addition, this aspect of the present invention relates to a nucleic acid molecule further comprising one or more expression control sequences controlling the transcription and/or translation of all or a part of a BSNA or the transcription and/or translation of a nucleic acid molecule that encodes all or a fragment of a BSP.

30 Another aspect of the present invention relates to vectors and/or host cells comprising a nucleic acid molecule of this invention. In a preferred embodiment, the nucleic acid molecule of the vector and/or host cell encodes all or a fragment of a BSP. In another preferred embodiment, the nucleic acid molecule of the vector and/or host cell

comprises all or a part of a BSNA. Vectors and host cells of the present invention are useful in the recombinant production of polypeptides, particularly BSPs of the present invention.

Another aspect of the present invention relates to polypeptides encoded by a nucleic acid molecule of this invention. The polypeptide may comprise either a fragment or a full-length protein. In a preferred embodiment, the polypeptide is a BSP. However, this aspect of the present invention also relates to mutant proteins (muteins) of BSPs, fusion proteins of which a portion is a BSP, and proteins and polypeptides encoded by allelic variants of a BSNA as provided herein.

A further aspect of the present invention is a novel splice variant which encodes an amino acid sequence that provides a novel region to be targeted for the generation of reagents that can be used in the detection and/or treatment of cancer. The novel amino acid sequence may lead to a unique protein structure, protein subcellular localization, biochemical processing or function. This information can be used to directly or indirectly facilitate the generation of additional or novel therapeutics or diagnostics. The nucleotide sequence in this novel splice variant can be used as a nucleic acid probe for the diagnosis and/or treatment of cancer.

Another aspect of the present invention relates to antibodies and other binders that specifically bind to a polypeptide of the instant invention. Accordingly antibodies or binders of the present invention specifically bind to BSPs, muteins, fusion proteins, and/or homologous proteins or polypeptides encoded by allelic variants of an BSNA as provided herein.

Another aspect of the present invention relates to agonists and antagonists of the nucleic acid molecules and polypeptides of this invention. The agonists and antagonists of the instant invention may be used to treat breast cancer and non-cancerous disease states in breast and to produce engineered breast tissue.

Another aspect of the present invention relates to methods for using the nucleic acid molecules to detect or amplify nucleic acid molecules that have similar or identical nucleic acid sequences compared to the nucleic acid molecules described herein. Such methods are useful in identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast. Such methods are also useful in identifying and/or monitoring breast tissue. In addition, measurement of levels of one or more of the nucleic acid molecules of this invention may be useful for diagnostics as part

of panel in combination with known other markers, particularly those described in the breast cancer background section above.

Another aspect of the present invention relates to use of the nucleic acid molecules of this invention in gene therapy, for producing transgenic animals and cells, and for

5 producing engineered breast tissue for treatment and research.

Another aspect of the present invention relates to methods for detecting polypeptides this invention, preferably using antibodies thereto. Such methods are useful to identify, diagnose, monitor, stage, image and treat breast cancer and non-cancerous disease states in breast. In addition, measurement of levels of one or more of the

10 polypeptides of this invention may be useful to identify, diagnose, monitor, stage, image breast cancer in combination with known other markers, particularly those described in the breast cancer background section above. The polypeptides of the present invention can also be used to identify and/or monitor breast tissue, and to produce engineered breast tissue.

15 Yet another aspect of the present invention relates to a computer readable means of storing the nucleic acid and amino acid sequences of the invention. The records of the computer readable means can be accessed for reading and displaying of sequences for comparison, alignment and ordering of the sequences of the invention to other sequences. In addition, the computer records regarding the nucleic acid and/or amino acid sequences 20 and/or measurements of their levels may be used alone or in combination with other markers to diagnose breast related diseases.

#### DETAILED DESCRIPTION OF THE INVENTION

##### Definitions and General Techniques

Unless otherwise defined herein, scientific and technical terms used in connection 25 with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid 30 chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various

general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press (1989) and Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 3d ed., Cold Spring Harbor Press (2001); 5 Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992, and Supplements to 2000); Ausubel *et al.*, Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology – 4<sup>th</sup> Ed., Wiley & Sons (1999); Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1990); and Harlow and Lane, Using Antibodies: A Laboratory Manual, 10 Cold Spring Harbor Laboratory Press (1999).

Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. 15

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

20 A "nucleic acid molecule" of this invention refers to a polymeric form of nucleotides and includes both sense and antisense strands of RNA, cDNA, genomic DNA, and synthetic forms and mixed polymers of the above. A nucleotide refers to a ribonucleotide, deoxynucleotide or a modified form of either type of nucleotide. A "nucleic acid molecule" as used herein is synonymous with "nucleic acid" and "polynucleotide." The term "nucleic acid molecule" usually refers to a molecule of at least 10 bases in length, unless otherwise specified. The term includes single and double stranded forms of DNA. In addition, a polynucleotide may include either or both naturally occurring and modified nucleotides linked together by naturally occurring and/or non-naturally occurring nucleotide linkages. 25

30 Nucleotides are represented by single letter symbols in nucleic acid molecule sequences. The following table lists symbols identifying nucleotides or groups of nucleotides that may occupy the symbol position on a nucleic acid molecule. See Nomenclature Committee of the International Union of Biochemistry (NC-IUB),

Nomenclature for incompletely specified bases in nucleic acid sequences,  
Recommendations 1984., *Eur J Biochem.* 150(1):1-5 (1985).

Symbol	Meaning	Group/Origin of Designation	Complementary Symbol
a	a	Adenine	t/u
g	g	Guanine	c
c	c	Cytosine	g
t	t	Thymine	a
u	u	Uracil	a
r	g or a	puRine	y
y	t/u or c	pYrimidine	r
m	a or c	aMino	k
k	g or t/u	Keto	m
s	g or c	Strong interactions 3H-bonds	w
w	a or t/u	Weak interactions 2H-bonds	s
b	g or c or t/u	not a	v
d	a or g or t/u	not c	h
h	a or c or t/u	not g	d
v	a or g or c	not t, not u	b
n	a or g or c or t/u, unknown, or other	any	n

- The nucleic acid molecules may be modified chemically or biochemically or may
- 5 contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those of skill in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.), charged linkages (e.g.,
- 10 phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g., polypeptides), intercalators (e.g., acridine, psoralen, etc.), chelators, alkylators, and modified linkages (e.g., alpha anomeric nucleic acids, etc.) The term "nucleic acid molecule" also includes any topological conformation, including single-stranded, double-stranded, partially duplexed, tripled, hairpinned, circular and padlocked conformations. Also included are
- 15 synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

- A "gene" is defined as a nucleic acid molecule that comprises a nucleic acid
- 20 sequence that encodes a polypeptide and the expression control sequences that surround the nucleic acid sequence that encodes the polypeptide. For instance, a gene may

comprise a promoter, one or more enhancers, a nucleic acid sequence that encodes a polypeptide, downstream regulatory sequences and, possibly, other nucleic acid sequences involved in regulation of the expression of an RNA. As is well known in the art, eukaryotic genes usually contain both exons and introns. The term "exon" refers to a 5 nucleic acid sequence found in genomic DNA that is bioinformatically predicted and/or experimentally confirmed to contribute contiguous sequence to a mature mRNA transcript. The term "intron" refers to a nucleic acid sequence found in genomic DNA that is predicted and/or confirmed to not contribute to a mature mRNA transcript, but rather to be "spliced out" during processing of the transcript.

10 A nucleic acid molecule or polypeptide is "derived" from a particular species if the nucleic acid molecule or polypeptide has been isolated from the particular species, or if the nucleic acid molecule or polypeptide is homologous to a nucleic acid molecule or polypeptide isolated from a particular species.

An "isolated" or "substantially pure" nucleic acid or polynucleotide (e.g., an RNA, 15 DNA or a mixed polymer) is one which is substantially separated from other cellular components that naturally accompany the native polynucleotide in its natural host cell, e.g., ribosomes, polymerases, or genomic sequences with which it is naturally associated. The term embraces a nucleic acid or polynucleotide that (1) has been removed from its naturally occurring environment, (2) is not associated with all or a portion of a 20 polynucleotide in which the "isolated polynucleotide" is found in nature, (3) is operatively linked to a polynucleotide which it is not linked to in nature, (4) does not occur in nature as part of a larger sequence or (5) includes nucleotides or internucleoside bonds that are not found in nature. The term "isolated" or "substantially pure" also can be used in reference to recombinant or cloned DNA isolates, chemically synthesized polynucleotide 25 analogs, or polynucleotide analogs that are biologically synthesized by heterologous systems. The term "isolated nucleic acid molecule" includes nucleic acid molecules that are integrated into a host cell chromosome at a heterologous site, recombinant fusions of a native fragment to a heterologous sequence, recombinant vectors present as episomes or as integrated into a host cell chromosome.

30 A "part" of a nucleic acid molecule refers to a nucleic acid molecule that comprises a partial contiguous sequence of at least 10 bases of the reference nucleic acid molecule. Preferably, a part comprises at least 15 to 20 bases of a reference nucleic acid molecule. In theory, a nucleic acid sequence of 17 nucleotides is of sufficient length to

- occur at random less frequently than once in the three gigabase human genome, and thus to provide a nucleic acid probe that can uniquely identify the reference sequence in a nucleic acid mixture of genomic complexity. A preferred part is one that comprises a nucleic acid sequence that can encode at least 6 contiguous amino acid sequences
- 5 (fragments of at least 18 nucleotides) because they are useful in directing the expression or synthesis of peptides that are useful in mapping the epitopes of the polypeptide encoded by the reference nucleic acid. *See, e.g., Geysen et al., Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1984); and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. A part may also comprise at
- 10 least 25, 30, 35 or 40 nucleotides of a reference nucleic acid molecule, or at least 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides of a reference nucleic acid molecule. A part of a nucleic acid molecule may comprise no other nucleic acid sequences. Alternatively, a part of a nucleic acid may comprise other nucleic acid sequences from other nucleic acid molecules.
- 15 The term "oligonucleotide" refers to a nucleic acid molecule generally comprising a length of 200 bases or fewer. The term often refers to single-stranded deoxyribonucleotides, but it can refer as well to single-or double-stranded ribonucleotides, RNA:DNA hybrids and double-stranded DNAs, among others. Preferably, oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17,
- 20 18, 19 or 20 bases in length. Other preferred oligonucleotides are 25, 30, 35, 40, 45, 50, 55 or 60 bases in length. Oligonucleotides may be single-stranded, *e.g.* for use as probes or primers, or may be double-stranded, *e.g.* for use in the construction of a mutant gene. Oligonucleotides of the invention can be either sense or antisense oligonucleotides. An oligonucleotide can be derivatized or modified as discussed above for nucleic acid
- 25 molecules.

Oligonucleotides, such as single-stranded DNA probe oligonucleotides, often are synthesized by chemical methods, such as those implemented on automated oligonucleotide synthesizers. However, oligonucleotides can be made by a variety of other methods, including *in vitro* recombinant DNA-mediated techniques and by

30 expression of DNAs in cells and organisms. Initially, chemically synthesized DNAs typically are obtained without a 5' phosphate. The 5' ends of such oligonucleotides are not substrates for phosphodiester bond formation by ligation reactions that employ DNA ligases typically used to form recombinant DNA molecules. Where ligation of such

oligonucleotides is desired, a phosphate can be added by standard techniques, such as those that employ a kinase and ATP. The 3' end of a chemically synthesized oligonucleotide generally has a free hydroxyl group and, in the presence of a ligase, such as T4 DNA ligase, readily will form a phosphodiester bond with a 5' phosphate of another polynucleotide, such as another oligonucleotide. As is well known, this reaction can be prevented selectively, where desired, by removing the 5' phosphates of the other polynucleotide(s) prior to ligation.

The term "naturally occurring nucleotide" referred to herein includes naturally occurring deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "nucleotide linkages" referred to herein includes nucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranylinate, phosphoroamidate, and the like. See e.g., LaPlanche *et al.* *Nucl. Acids Res.* 14:9081-9093 (1986); Stein *et al.* *Nucl. Acids Res.* 16:3209-3221 (1988); Zon *et al.* *Anti-Cancer Drug Design* 6:539-568 (1991); Zon *et al.*, in Eckstein (ed.) Oligonucleotides and Analogues: A Practical Approach, pp. 87-108, Oxford University Press (1991); Uhlmann and Peyman *Chemical Reviews* 90:543 (1990), and U.S. Patent No. 5,151,510, the disclosure of which is hereby incorporated by reference in its entirety.

Unless specified otherwise, the left hand end of a polynucleotide sequence in sense orientation is the 5' end and the right hand end of the sequence is the 3' end. In addition, the left hand direction of a polynucleotide sequence in sense orientation is referred to as the 5' direction, while the right hand direction of the polynucleotide sequence is referred to as the 3' direction. Further, unless otherwise indicated, each nucleotide sequence is set forth herein as a sequence of deoxyribonucleotides. It is intended, however, that the given sequence be interpreted as would be appropriate to the polynucleotide composition: for example, if the isolated nucleic acid is composed of RNA, the given sequence intends ribonucleotides, with uridine substituted for thymidine.

The term "allelic variant" refers to one of two or more alternative naturally occurring forms of a gene, wherein each gene possesses a unique nucleotide sequence. In a preferred embodiment, different alleles of a given gene have similar or identical biological properties.

The term "percent sequence identity" in the context of nucleic acid sequences refers to the residues in two sequences that are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least 5 about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different algorithms known in the art that can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap or Bestfit, which are programs in Wisconsin Package Version 10.0, Genetics Computer 10 Group (GCG), Madison, Wisconsin. FASTA, which includes, e.g., the programs FASTA2 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183: 63-98 (1990); Pearson, *Methods Mol. Biol.* 132: 185-219 (2000); Pearson, *Methods Enzymol.* 266: 227-258 (1996); Pearson, *J. Mol. Biol.* 276: 71-84 (1998)). Unless otherwise 15 specified, default parameters for a particular program or algorithm are used. For instance, percent sequence identity between nucleic acid sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in GCG Version 6.1.

A reference to a nucleic acid sequence encompasses its complement unless 20 otherwise specified. Thus, a reference to a nucleic acid molecule having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence. The complementary strand is also useful, e.g., for antisense therapy, double stranded RNA (dsRNA) inhibition (RNAi), combination of triplex and antisense, hybridization probes and PCR primers.

In the molecular biology art, researchers use the terms "percent sequence identity", "percent sequence similarity" and "percent sequence homology" interchangeably. In this 25 application, these terms shall have the same meaning with respect to nucleic acid sequences only.

The term "substantial similarity" or "substantial sequence similarity," when 30 referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 50%, more preferably 60% of the nucleotide bases, usually at least about 70%, more usually at least

about 80%, preferably at least about 90%, and more preferably at least about 95-98% of the nucleotide bases, as measured by any well known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed above.

Alternatively, substantial similarity exists between a first and second nucleic acid sequence when the first nucleic acid sequence or fragment thereof hybridizes to an antisense strand of the second nucleic acid, under selective hybridization conditions. Typically, selective hybridization will occur between the first nucleic acid sequence and an antisense strand of the second nucleic acid sequence when there is at least about 55% sequence identity between the first and second nucleic acid sequences—preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%—over a stretch of at least about 14 nucleotides, more preferably at least 17 nucleotides, even more preferably at least 20, 25, 30, 35, 40, 50, 60, 70, 80, 90 or 100 nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, solvents, the base composition of the hybridizing species, length of the complementary regions, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. “Stringent hybridization conditions” and “stringent wash conditions” in the context of nucleic acid hybridization experiments depend upon a number of different physical parameters. The most important parameters include temperature of hybridization, base composition of the nucleic acids, salt concentration and length of the nucleic acid. One having ordinary skill in the art knows how to vary these parameters to achieve a particular stringency of hybridization. In general, “stringent hybridization” is performed at about 25°C below the thermal melting point ( $T_m$ ) for the specific DNA hybrid under a particular set of conditions. “Stringent washing” is performed at temperatures about 5°C lower than the  $T_m$  for the specific DNA hybrid under a particular set of conditions. The  $T_m$  is the temperature at which 50% of the target sequence hybridizes to a perfectly matched probe.

See Sambrook (1989), *supra*, p. 9.51.

The  $T_m$  for a particular DNA-DNA hybrid can be estimated by the formula:

$$T_m = 81.5^\circ\text{C} + 16.6 (\log_{10}[\text{Na}^+]) + 0.41 (\text{fraction G} + \text{C}) -$$

30 0.63 (% formamide) - (600/l) where l is the length of the hybrid in base pairs.

The  $T_m$  for a particular RNA-RNA hybrid can be estimated by the formula:

$$T_m = 79.8^\circ\text{C} + 18.5 (\log_{10}[\text{Na}^+]) + 0.58 (\text{fraction G} + \text{C}) + 11.8 (\text{fraction G} + \text{C})^2 - 0.35 (% \text{ formamide}) - (820/l).$$

The  $T_m$  for a particular RNA-DNA hybrid can be estimated by the formula:

$$T_m = 79.8^\circ\text{C} + 18.5(\log_{10}[\text{Na}^+]) + 0.58 \text{ (fraction G + C)} + \\ 11.8 \text{ (fraction G + C)}^2 - 0.50 \text{ (% formamide)} - (820/I).$$

In general, the  $T_m$  decreases by 1-1.5°C for each 1% of mismatch between two

- 5 nucleic acid sequences. Thus, one having ordinary skill in the art can alter hybridization and/or washing conditions to obtain sequences that have higher or lower degrees of sequence identity to the target nucleic acid. For instance, to obtain hybridizing nucleic acids that contain up to 10% mismatch from the target nucleic acid sequence, 10-15°C would be subtracted from the calculated  $T_m$  of a perfectly matched hybrid, and then the  
10 hybridization and washing temperatures adjusted accordingly. Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

- An example of stringent hybridization conditions for hybridization of  
15 complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or Northern blot or for screening a library is 50% formamide/6X SSC at 42°C for at least ten hours and preferably overnight (approximately 16 hours). Another example of stringent hybridization conditions is 6X SSC at 68°C without formamide for at least ten hours and preferably overnight. An example of moderate stringency  
20 hybridization conditions is 6X SSC at 55°C without formamide for at least ten hours and preferably overnight. An example of low stringency hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or northern blot or for screening a library is 6X SSC at 42°C for at least ten hours. Hybridization conditions to identify nucleic acid  
25 sequences that are similar but not identical can be identified by experimentally changing the hybridization temperature from 68°C to 42°C while keeping the salt concentration constant (6X SSC), or keeping the hybridization temperature and salt concentration constant (e.g. 42°C and 6X SSC) and varying the formamide concentration from 50% to 0%. Hybridization buffers may also include blocking agents to lower background. These  
30 agents are well known in the art. See Sambrook *et al.* (1989), *supra*, pages 8.46 and 9.46-9.58. See also Ausubel (1992), *supra*, Ausubel (1999), *supra*, and Sambrook (2001), *supra*.

Wash conditions also can be altered to change stringency conditions. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (*see* Sambrook (1989), *supra*, for SSC buffer). Often the high stringency wash is preceded by a low stringency wash to remove excess probe. An exemplary medium stringency wash for duplex DNA of more than 100 base pairs is 1x SSC at 45°C for 15 minutes. An exemplary low stringency wash for such a duplex is 4x SSC at 40°C for 15 minutes. In general, signal-to-noise ratio of 2x or higher than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization.

As defined herein, nucleic acids that do not hybridize to each other under stringent conditions are still substantially similar to one another if they encode polypeptides that are substantially identical to each other. This occurs, for example, when a nucleic acid is created synthetically or recombinantly using a high codon degeneracy as permitted by the redundancy of the genetic code.

Hybridization conditions for nucleic acid molecules that are shorter than 100 nucleotides in length (*e.g.*, for oligonucleotide probes) may be calculated by the formula:

$T_m = 81.5^\circ\text{C} + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\text{fraction G+C}) - (600/N)$ , wherein N is change length and the  $[\text{Na}^+]$  is 1 M or less. *See* Sambrook (1989), *supra*, p. 11.46. For hybridization of probes shorter than 100 nucleotides, hybridization is usually performed under stringent conditions (5-10°C below the  $T_m$ ) using high concentrations (0.1-1.0 pmol/ml) of probe. *Id.* at p. 11.45. Determination of hybridization using mismatched probes, pools of degenerate probes or "guessmers," as well as hybridization solutions and methods for empirically determining hybridization conditions are well known in the art. *See, e.g.*, Ausubel (1999), *supra*; Sambrook (1989), *supra*, pp. 11.45-11.57.

The term "digestion" or "digestion of DNA" refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes referred to herein are commercially available and their reaction conditions, cofactors and other requirements for use are known and routine to the skilled artisan. For analytical purposes, typically, 1 µg of plasmid or DNA fragment is digested with about 2 units of enzyme in about 20 µl of reaction buffer. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 µg of DNA are digested with 20 to 250 units of enzyme in proportionately larger volumes. Appropriate buffers and substrate amounts for particular restriction enzymes are described in standard laboratory manuals, such as those referenced below, and are specified by commercial

suppliers. Incubation times of about 1 hour at 37°C are ordinarily used, but conditions may vary in accordance with standard procedures, the supplier's instructions and the particulars of the reaction. After digestion, reactions may be analyzed, and fragments may be purified by electrophoresis through an agarose or polyacrylamide gel, using well-known methods that are routine for those skilled in the art.

5 The term "ligation" refers to the process of forming phosphodiester bonds between two or more polynucleotides, which most often are double-stranded DNAs. Techniques for ligation are well known to the art and protocols for ligation are described in standard laboratory manuals and references, such as, e.g., Sambrook (1989), *supra*.

10 Genome-derived "single exon probes," are probes that comprise at least part of an exon ("reference exon") and can hybridize detectably under high stringency conditions to transcript-derived nucleic acids that include the reference exon but do not hybridize detectably under high stringency conditions to nucleic acids that lack the reference exon. Single exon probes typically further comprise, contiguous to a first end of the exon portion, a first intronic and/or intergenic sequence that is identically contiguous to the exon in the genome, and may contain a second intronic and/or intergenic sequence that is identically contiguous to the exon in the genome. The minimum length of genome-derived single exon probes is defined by the requirement that the exonic portion be of sufficient length to hybridize under high stringency conditions to transcript-derived nucleic acids, as discussed above. The maximum length of genome-derived single exon probes is defined by the requirement that the probes contain portions of no more than one exon. The single exon probes may contain priming sequences not found in contiguity with the rest of the probe sequence in the genome, which priming sequences are useful for PCR and other amplification-based technologies. In another aspect, the invention is directed to 20 single exon probes based on the BSNA disclosed herein.

15

25 In one embodiment, the term "microarray" refers to a "nucleic acid microarray" having a substrate-bound plurality of nucleic acids, hybridization to each of the plurality of bound nucleic acids being separately detectable. The substrate can be solid or porous, planar or non-planar, unitary or distributed. Nucleic acid microarrays include all the devices so called in Schena (ed.), DNA Microarrays: A Practical Approach (Practical Approach Series), Oxford University Press (1999); *Nature Genet.* 21(1)(suppl.):1 - 60 (1999); Schena (ed.), Microarray Biochip: Tools and Technology, Eaton Publishing Company/BioTechniques Books Division (2000). Additionally, these nucleic acid

microarrays include substrate-bound plurality of nucleic acids in which the plurality of nucleic acids are disposed on a plurality of beads, rather than on a unitary planar substrate, as is described, *inter alia*, in Brenner *et al.*, *Proc. Natl. Acad. Sci. USA* 97(4):1665-1670 (2000). Examples of nucleic acid microarrays may be found in U.S. Patent Nos. 5 6,391,623, 6,383,754, 6,383,749, 6,380,377, 6,379,897, 6,376,191, 6,372,431, 6,351,712, 6,344,316, 6,316,193, 6,312,906, 6,309,828, 6,309,824, 6,306,643, 6,300,063, 6,287,850, 6,284,497, 6,284,465, 6,280,954, 6,262,216, 6,251,601, 6,245,518, 6,263,287, 6,251,601, 6,238,866, 6,228,575, 6,214,587, 6,203,989, 6,171,797, 6,103,474, 6,083,726, 6,054,274, 6,040,138, 6,083,726, 6,004,755, 6,001,309, 5,958,342, 5,952,180, 5,936,731, 5,843,655, 10 5,814,454, 5,837,196, 5,436,327, 5,412,087, 5,405,783, the disclosures of which are incorporated herein by reference in their entireties.

In an alternative embodiment, a "microarray" may also refer to a "peptide microarray" or "protein microarray" having a substrate-bound collection of plurality of polypeptides, the binding to each of the plurality of bound polypeptides being separately detectable. Alternatively, the peptide microarray ,may have a plurality of binders, including but not limited to monoclonal antibodies, polyclonal antibodies, phage display binders, yeast 2 hybrid binders, aptamers, which can specifically detect the binding of the polypeptides of this invention. The array may be based on autoantibody detection to the polypeptides of this invention, see Robinson *et al.*, *Nature Medicine* 8(3):295-301 (2002). Examples of peptide arrays may be found in WO 02/31463, WO 02/25288, WO 01/94946, 15 WO 01/88162, WO 01/68671, WO 01/57259, WO 00/61806, WO 00/54046, WO 00/47774, WO 99/40434, WO 99/39210, WO 97/42507 and U.S. Patent Nos. 6,268,210, 20 5,766,960, 5,143,854, the disclosures of which are incorporated herein by reference in their entireties.

25 In addition, determination of the levels of the BSNA or BSP may be made in a multiplex manner using techniques described in WO 02/29109, WO 02/24959, WO 01/83502, WO01/73113, WO 01/59432, WO 01/57269, WO 99/67641, the disclosures of which are incorporated herein by reference in their entireties.

The term "mutant", "mutated", or "mutation" when applied to nucleic acid 30 sequences means that nucleotides in a nucleic acid sequence may be inserted, deleted or changed compared to a reference nucleic acid sequence. A single alteration may be made at a locus (a point mutation) or multiple nucleotides may be inserted, deleted or changed at a single locus. In addition, one or more alterations may be made at any number of loci

within a nucleic acid sequence. In a preferred embodiment of the present invention, the nucleic acid sequence is the wild type nucleic acid sequence encoding a BSP or is a BSNA. The nucleic acid sequence may be mutated by any method known in the art, including those mutagenesis techniques described *infra*.

5       The term “error-prone PCR” refers to a process for performing PCR under conditions where the copying fidelity of the DNA polymerase is low, such that a high rate of point mutations is obtained along the entire length of the PCR product. *See, e.g.*, Leung *et al.*, *Technique* 1: 11-15 (1989) and Caldwell *et al.*, *PCR Methods Applic.* 2: 28-33 (1992).

10      The term “oligonucleotide-directed mutagenesis” refers to a process that enables the generation of site-specific mutations in any cloned DNA segment of interest. *See, e.g.*, Reidhaar-Olson *et al.*, *Science* 241: 53-57 (1988).

15      The term “assembly PCR” refers to a process that involves the assembly of a PCR product from a mixture of small DNA fragments. A large number of different PCR reactions occur in parallel in the same vial, with the products of one reaction priming the products of another reaction.

20      The term “sexual PCR mutagenesis” or “DNA shuffling” refers to a method of error-prone PCR coupled with forced homologous recombination between DNA molecules of different but highly related DNA sequence *in vitro*, caused by random fragmentation of the DNA molecule based on sequence similarity, followed by fixation of the crossover by primer extension in an error-prone PCR reaction. *See, e.g.*, Stemmer, *Proc. Natl. Acad. Sci. U.S.A.* 91: 10747-10751 (1994). DNA shuffling can be carried out between several related genes (“Family shuffling”).

25      The term “*in vivo* mutagenesis” refers to a process of generating random mutations in any cloned DNA of interest which involves the propagation of the DNA in a strain of bacteria such as *E. coli* that carries mutations in one or more of the DNA repair pathways. These “mutator” strains have a higher random mutation rate than that of a wild-type parent. Propagating the DNA in a mutator strain will eventually generate random mutations within the DNA.

30      The term “cassette mutagenesis” refers to any process for replacing a small region of a double-stranded DNA molecule with a synthetic oligonucleotide “cassette” that differs from the native sequence. The oligonucleotide often contains completely and/or partially randomized native sequence.

The term "recursive ensemble mutagenesis" refers to an algorithm for protein engineering (protein mutagenesis) developed to produce diverse populations of phenotypically related mutants whose members differ in amino acid sequence. This method uses a feedback mechanism to control successive rounds of combinatorial cassette mutagenesis. See, e.g., Arkin *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 89: 7811-7815 (1992).

5 The term "exponential ensemble mutagenesis" refers to a process for generating combinatorial libraries with a high percentage of unique and functional mutants, wherein small groups of residues are randomized in parallel to identify, at each altered position, amino acids that lead to functional proteins. See, e.g., Delegrave *et al.*, *Biotechnology Research* 11: 1548-1552 (1993); Arnold, *Current Opinion in Biotechnology* 4: 450-455 (1993).

10 "Operatively linked" expression control sequences refers to a linkage in which the expression control sequence is either contiguous with the gene of interest to control the gene of interest, or acts in *trans* or at a distance to control the gene of interest.

15 The term "expression control sequence" as used herein refers to polynucleotide sequences that are necessary to affect the expression of coding sequences to which they are operatively linked. Expression control sequences are sequences that control the transcription, post-transcriptional events and translation of nucleic acid sequences. Expression control sequences include appropriate transcription initiation, termination, 20 promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (e.g., ribosome binding sites); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such 25 control sequences generally include promoter, ribosomal binding site, and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

30 The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Other vectors include cosmids, bacterial

- artificial chromosomes (BAC) and yeast artificial chromosomes (YAC). Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Viral vectors that infect bacterial cells are referred to as bacteriophages. Certain vectors are capable of autonomous replication in a host cell into which they are introduced
- 5       (e.g., bacterial vectors having a bacterial origin of replication). Other vectors can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors").
- 10      In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include other forms of expression vectors that serve equivalent functions.
- 15      The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny
- 20      may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.
- As used herein, the phrase "open reading frame" and the equivalent acronym "ORF" refers to that portion of a transcript-derived nucleic acid that can be translated in its entirety into a sequence of contiguous amino acids. As so defined, an ORF has length,
- 25      measured in nucleotides, exactly divisible by 3. As so defined, an ORF need not encode the entirety of a natural protein.
- As used herein, the phrase "ORF-encoded peptide" refers to the predicted or actual translation of an ORF.
- As used herein, the phrase "degenerate variant" of a reference nucleic acid
- 30      sequence is meant to be inclusive of all nucleic acid sequences that can be directly translated, using the standard genetic code, to provide an amino acid sequence identical to that translated from the reference nucleic acid sequence.

The term "polypeptide" encompasses both naturally occurring and non-naturally occurring proteins and polypeptides, as well as polypeptide fragments and polypeptide mutants, derivatives and analogs thereof. A polypeptide may be monomeric or polymeric.

5 Further, a polypeptide may comprise a number of different modules within a single polypeptide each of which has one or more distinct activities. A preferred polypeptide in accordance with the invention comprises a BSP encoded by a nucleic acid molecule of the instant invention, or a fragment, mutant, analog and derivative thereof.

The term "isolated protein" or "isolated polypeptide" is a protein or polypeptide that by virtue of its origin or source of derivation (1) is not associated with naturally 10 associated components that accompany it in its native state, (2) is free of other proteins from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" 15 from its naturally associated components. A polypeptide or protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

A protein or polypeptide is "substantially pure," "substantially homogeneous" or "substantially purified" when at least about 60% to 75% of a sample exhibits a single species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A 20 substantially pure polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be determined by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a stain well 25 known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The term "fragment" when used herein with respect to polypeptides of the present invention refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion compared to a full-length BSP. In a preferred embodiment, the fragment is a 30 contiguous sequence in which the amino acid sequence of the fragment is identical to the corresponding positions in the naturally occurring polypeptide. Fragments typically are at least 5, 6, 7, 8, 9 or 10 amino acids long, preferably at least 12, 14, 16 or 18 amino acids long, more preferably at least 20 amino acids long, more preferably at least 25, 30, 35, 40

or 45, amino acids, even more preferably at least 50 or 60 amino acids long, and even more preferably at least 70 amino acids long.

A "derivative" when used herein with respect to polypeptides of the present invention refers to a polypeptide which is substantially similar in primary structural sequence to a BSP but which include, *e.g.*, *in vivo* or *in vitro* chemical and biochemical modifications that are not found in the BSP. Such modifications include, for example, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Other modification include, *e.g.*, labeling with radionuclides, and various enzymatic modifications, as will be readily appreciated by those skilled in the art. A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes are well known in the art, and include radioactive isotopes such as  $^{125}\text{I}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$  and  $^3\text{H}$ , ligands which bind to labeled antiligands (*e.g.*, antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required, ease of conjugation with the primer, stability requirements, and available instrumentation. Methods for labeling polypeptides are well known in the art. *See Ausubel (1992), supra; Ausubel (1999), supra.*

The term "fusion protein" refers to polypeptides of the present invention coupled to a heterologous amino acid sequences. Fusion proteins are useful because they can be constructed to contain two or more desired functional elements from two or more different proteins. A fusion protein comprises at least 10 contiguous amino acids from a polypeptide of interest, more preferably at least 20 or 30 amino acids, even more preferably at least 40, 50 or 60 amino acids, yet more preferably at least 75, 100 or 125 amino acids. Fusion proteins can be produced recombinantly by constructing a nucleic acid sequence that encodes the polypeptide or a fragment thereof in frame with a nucleic

acid sequence encoding a different protein or peptide and then expressing the fusion protein. Alternatively, a fusion protein can be produced chemically by crosslinking the polypeptide or a fragment thereof to another protein.

The term "analog" refers to both polypeptide analogs and non-peptide analogs.

- 5     The term "polypeptide analog" as used herein refers to a polypeptide that is comprised of a segment of at least 25 amino acids that has substantial identity to a portion of an amino acid sequence but which contains non-natural amino acids or non-natural inter-residue bonds. In a preferred embodiment, the analog has the same or similar biological activity as the native polypeptide. Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the naturally occurring sequence.
- 10    Analog typically are at least 20 amino acids long, preferably at least 50 amino acids long or longer, and can often be as long as a full-length naturally occurring polypeptide.

15    The term "non-peptide analog" refers to a compound with properties that are analogous to those of a reference polypeptide. A non-peptide compound may also be termed a "peptide mimetic" or a "peptidomimetic." Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to useful peptides may be used to produce an equivalent effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a desired biochemical property or pharmacological activity), but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of:

20    --CH<sub>2</sub>NH--, --CH<sub>2</sub>S--, --CH<sub>2</sub>-CH<sub>2</sub>--, --CH=CH--(cis and trans), --COCH<sub>2</sub>--,  
      --CH(OH)CH<sub>2</sub>--, and --CH<sub>2</sub>SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo *et al.*, *Ann. Rev. Biochem.* 61:387-418 (1992)). For example, one may add internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

- 25    The term "mutant" or "mutein" when referring to a polypeptide of the present invention relates to an amino acid sequence containing substitutions, insertions or deletions of one or more amino acids compared to the amino acid sequence of a BSP. A

mutein may have one or more amino acid point substitutions, in which a single amino acid at a position has been changed to another amino acid, one or more insertions and/or deletions, in which one or more amino acids are inserted or deleted, respectively, in the sequence of the naturally occurring protein, and/or truncations of the amino acid sequence 5 at either or both the amino or carboxy termini. Further, a mutein may have the same or different biological activity as the naturally occurring protein. For instance, a mutein may have an increased or decreased biological activity. A mutein has at least 50% sequence similarity to the wild type protein, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are muteins having 80%, 85% or 90% 10 sequence similarity to a BSP. In an even more preferred embodiment, a mutein exhibits 95% sequence identity, even more preferably 97%, even more preferably 98% and even more preferably 99%. Sequence similarity may be measured by any common sequence analysis algorithm, such as GAP or BESTFIT or other variation Smith-Waterman alignment. *See*, T. F. Smith and M. S. Waterman, *J. Mol. Biol.* 147:195-197 (1981) and 15 W.R. Pearson, *Genomics* 11:635-650 (1991).

Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinity or enzymatic activity, and (5) confer or modify other physicochemical or functional properties of such analogs. For example, 20 single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. In a preferred embodiment, the amino acid substitutions are moderately conservative substitutions or conservative substitutions. In a more preferred embodiment, the amino acid substitutions 25 are conservative substitutions. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not tend to disrupt a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are 30 described in Creighton (ed.), Proteins, Structures and Molecular Principles, W. H. Freeman and Company (1984); Branden *et al.* (ed.), Introduction to Protein Structure, Garland Publishing (1991); Thornton *et al.*, *Nature* 354:105-106 (1991).

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See Golub *et al.* (eds.), Immunology - A Synthesis 2<sup>nd</sup> Ed., Sinauer Associates (1991). Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as  $\alpha$ -,  $\alpha$ -disubstituted amino acids, N-alkyl amino acids, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline,  $\gamma$ -carboxyglutamate,  $\epsilon$ -N,N,N-trimethyllysine,  $\epsilon$ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, s-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

By "homology" or "homologous" when referring to a polypeptide of the present invention it is meant polypeptides from different organisms with a similar sequence to the encoded amino acid sequence of a BSP and a similar biological activity or function. Although two polypeptides are said to be "homologous," this does not imply that there is necessarily an evolutionary relationship between the polypeptides. Instead, the term "homologous" is defined to mean that the two polypeptides have similar amino acid sequences and similar biological activities or functions. In a preferred embodiment, a homologous polypeptide is one that exhibits 50% sequence similarity to BSP, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are homologous polypeptides that exhibit 80%, 85% or 90% sequence similarity to a BSP. In a yet more preferred embodiment, a homologous polypeptide exhibits 95%, 97%, 98% or 99% sequence similarity.

When "sequence similarity" is used in reference to polypeptides, it is recognized that residue positions that are not identical often differ by conservative amino acid substitutions. In a preferred embodiment, a polypeptide that has "sequence similarity" comprises conservative or moderately conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (*e.g.*, charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative

substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. *See, e.g., Pearson, Methods Mol. Biol.* 24: 307-31 (1994).

5 For instance, the following six groups each contain amino acids that are conservative substitutions for one another:

- 1) Serine (S), Threonine (T);
- 2) Aspartic Acid (D), Glutamic Acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 10 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Alanine (A), Valine (V), and
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.*, *Science* 256: 1443-45  
15 (1992). A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions,  
20 deletions and other modifications, including conservative amino acid substitutions. For instance, GCG contains programs such as "Gap" and "Bestfit" which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. *See, e.g., GCG Version*  
25 6.1. Other programs include FASTA, discussed *supra*.

A preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn. *See, e.g., Altschul *et al.*, J. Mol. Biol.* 215: 403-410 (1990); Altschul *et al.*, *Nucleic Acids Res.* 25:3389-402 (1997). Preferred parameters for  
30 blastp are:

- Expectation value: 10 (default)  
Filter: seg (default)  
Cost to open a gap: 11 (default)

Cost to extend a gap: 1 (default)  
Max. alignments: 100 (default)  
Word size: 11 (default)  
No. of descriptions: 100 (default)

5 Penalty Matrix: BLOSUM62

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number of 10 different organisms, it is preferable to compare amino acid sequences.

Algorithms other than blastp for database searching using amino acid sequences are known in the art. For instance, polypeptide sequences can be compared using FASTA, a program in GCG Version 6.1. FASTA (*e.g.*, FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the 15 query and search sequences (Pearson (1990), *supra*; Pearson (2000), *supra*). For example, percent sequence identity between amino acid sequences can be determined using FASTA with its default or recommended parameters (a word size of 2 and the PAM250 scoring matrix), as provided in GCG Version 6.1.

An “antibody” refers to an intact immunoglobulin, or to an antigen-binding portion 20 thereof that competes with the intact antibody for specific binding to a molecular species, *e.g.*, a polypeptide of the instant invention. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies.

Antigen-binding portions include, *inter alia*, Fab, Fab', F(ab')<sub>2</sub>, Fv, dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), 25 chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. A Fab fragment is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab')<sub>2</sub> fragment is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consists of the VH and CH1 domains; a Fv fragment consists of the VL and VH domains of a single arm of an antibody; and a dAb 30 fragment consists of a VH domain. *See, e.g.*, Ward *et al.*, *Nature* 341: 544-546 (1989).

By “bind specifically” and “specific binding” as used herein it is meant the ability of the antibody to bind to a first molecular species in preference to binding to other

molecular species with which the antibody and first molecular species are admixed. An antibody is said specifically to "recognize" a first molecular species when it can bind specifically to that first molecular species.

A single-chain antibody (scFv) is an antibody in which VL and VH regions are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain. *See, e.g., Bird et al., Science 242: 423-426 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85: 5879-5883 (1988).* Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites. *See e.g., Holliger et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993); Poljak et al., Structure 2: 1121-1123 (1994).* One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest. A chimeric antibody is an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies.

An antibody may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally occurring immunoglobulin has two identical binding sites, a single-chain antibody or Fab fragment has one binding site, while a "bispecific" or "bifunctional" antibody has two different binding sites.

An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. It is known that purified proteins, including purified antibodies, may be stabilized with non-naturally-associated components. The non-naturally-associated component may be a protein, such as albumin (*e.g.*, BSA) or a chemical such as polyethylene glycol (PEG).

A "neutralizing antibody" or "an inhibitory antibody" is an antibody that inhibits the activity of a polypeptide or blocks the binding of a polypeptide to a ligand that

normally binds to it. An "activating antibody" is an antibody that increases the activity of a polypeptide.

The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is less than 1  $\mu\text{M}$ , preferably less than 100 nM and most preferably less than 10 nM.

10 The term "patient" includes human and veterinary subjects.

Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

15 The term "breast specific" refers to a nucleic acid molecule or polypeptide that is expressed predominantly in the breast as compared to other tissues in the body. In a preferred embodiment, a "breast specific" nucleic acid molecule or polypeptide is detected at a level that is 1.5-fold higher than any other tissue in the body. In a more preferred embodiment, the "breast specific" nucleic acid molecule or polypeptide is detected at a level that is 2-fold higher than any other tissue in the body, more preferably 5-fold higher, 20 still more preferably at least 10-fold, 15-fold, 20-fold, 25-fold, 50-fold or 100-fold higher than any other tissue in the body. Nucleic acid molecule levels may be measured by nucleic acid hybridization, such as Northern blot hybridization, or quantitative PCR. Polypeptide levels may be measured by any method known to accurately quantitate protein levels, such as Western blot analysis.

25 Nucleic Acid Molecules, Regulatory Sequences, Vectors, Host Cells and Recombinant Methods of Making Polypeptides

*Nucleic Acid Molecules*

One aspect of the invention provides isolated nucleic acid molecules that are specific to the breast or to breast cells or tissue or that are derived from such nucleic acid 30 molecules. These isolated breast specific nucleic acids (BSNAs) may comprise cDNA, genomic DNA, RNA, or a combination thereof, a fragment of one of these nucleic acids, or may be a non-naturally occurring nucleic acid molecule. A BSNA may be derived from

an animal. In a preferred embodiment, the BSNA is derived from a human or other mammal. In a more preferred embodiment, the BSNA is derived from a human or other primate. In an even more preferred embodiment, the BSNA is derived from a human.

In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that  
5 is specific to breast, a breast-specific polypeptide (BSP). In a more preferred embodiment, the nucleic acid molecule encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 95-156. In another highly preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-94. Nucleotide sequences of the instantly described nucleic acid molecules were determined by assembling several DNA  
10 molecules from either public or proprietary databases. Some of the underlying DNA sequences are the result, directly or indirectly, of at least one enzymatic polymerization reaction (*e.g.*, reverse transcription and/or polymerase chain reaction) using an automated sequencer (such as the MegaBACE™ 1000, Amersham Biosciences, Sunnyvale, CA, USA).

Nucleic acid molecules of the present invention may also comprise sequences that selectively hybridizes to a nucleic acid molecule encoding a BSNA or a complement or antisense thereof. The hybridizing nucleic acid molecule may or may not encode a polypeptide or may or may not encode a BSP. However, in a preferred embodiment, the hybridizing nucleic acid molecule encodes a BSP. In a more preferred embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 95-156. In an even more preferred embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 1-94 or the antisense sequence thereof. Preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a BSP under low stringency conditions. More preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a BSP under moderate stringency conditions. Most preferably,  
20 the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a BSP under high stringency conditions. In a preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule or the antisense sequence of a nucleic  
25  
30

acid molecule encoding a polypeptide comprising an amino acid sequence of SEQ ID NO: 95-156. In a more preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule comprising a nucleic acid sequence selected from

5 SEQ ID NO: 1-94.

Nucleic acid molecules of the present invention may also comprise nucleic acid sequences that exhibit substantial sequence similarity to a nucleic acid encoding a BSP or a complement of the encoding nucleic acid molecule. In this embodiment, it is preferred that the nucleic acid molecule exhibit substantial sequence similarity to a nucleic acid 10 molecule encoding human BSP. More preferred is a nucleic acid molecule exhibiting substantial sequence similarity to a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 95-156. By substantial sequence similarity it is meant a nucleic acid molecule having at least 60% sequence identity with a nucleic acid molecule encoding a BSP, such as a polypeptide having an amino acid sequence of SEQ 15 ID NO: 95-156, more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85%. In a more preferred embodiment, the similar nucleic acid molecule is one that has at least 90% sequence identity with a nucleic acid molecule encoding a BSP, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%. Most preferred in this 20 embodiment is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a nucleic acid molecule encoding a BSP.

The nucleic acid molecules of the present invention are also inclusive of those exhibiting substantial sequence similarity to a BSNA or its complement. In this embodiment, it is preferred that the nucleic acid molecule exhibit substantial sequence 25 similarity to a nucleic acid molecule having a nucleic acid sequence of SEQ ID NO: 1-94. By substantial sequence similarity it is meant a nucleic acid molecule that has at least 60% sequence identity with a BSNA, such as one having a nucleic acid sequence of SEQ ID NO: 1-94, more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85%. More preferred is a nucleic acid molecule that has at least 90% 30 sequence identity with a BSNA, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%. Most preferred is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a BSNA.

Nucleic acid molecules that exhibit substantial sequence similarity are inclusive of sequences that exhibit sequence identity over their entire length to a BSNA or to a nucleic acid molecule encoding a BSP, as well as sequences that are similar over only a part of its length. In this case, the part is at least 50 nucleotides of the BSNA or the nucleic acid 5 molecule encoding a BSP, preferably at least 100 nucleotides, more preferably at least 150 or 200 nucleotides, even more preferably at least 250 or 300 nucleotides, still more preferably at least 400 or 500 nucleotides.

The substantially similar nucleic acid molecule may be a naturally occurring one that is derived from another species, especially one derived from another primate, wherein 10 the similar nucleic acid molecule encodes an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 95-156 or demonstrates significant sequence identity to the nucleotide sequence of SEQ ID NO: 1-94. The similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule from a human, when the BSNA is a member of a gene family. The similar nucleic acid molecule may also be a 15 naturally occurring nucleic acid molecule derived from a non-primate, mammalian species, including without limitation, domesticated species, e.g., dog, cat, mouse, rat, rabbit, hamster, cow, horse and pig; and wild animals, e.g., monkey, fox, lions, tigers, bears, giraffes, zebras, etc. The substantially similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule derived from a non-mammalian species, such as 20 birds or reptiles. The naturally occurring substantially similar nucleic acid molecule may be isolated directly from humans or other species. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by random mutation of a nucleic acid molecule. In another embodiment, the substantially 25 similar nucleic acid molecule may be one that is experimentally produced by directed mutation of a BSNA. In a preferred embodiment, the substantially similar nucleic acid molecule is an BSNA.

The nucleic acid molecules of the present invention are also inclusive of allelic variants of a BSNA or a nucleic acid encoding a BSP. For example, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes and the sequence 30 determined from one individual of a species may differ from other allelic forms present within the population. More than 1.4 million SNPs have already identified in the human genome, International Human Genome Sequencing Consortium, *Nature* 409: 860-921 (2001) – Variants with small deletions and insertions of more than a single nucleotide are

also found in the general population, and often do not alter the function of the protein. In addition, amino acid substitutions occur frequently among natural allelic variants, and often do not substantially change protein function.

In a preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that encodes a BSP. In a more preferred embodiment, the gene is transcribed into an mRNA that encodes a BSP comprising an amino acid sequence of SEQ ID NO: 95-156. In another preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that is a BSNA. In a more preferred embodiment, the gene is transcribed into an mRNA that comprises the nucleic acid sequence of SEQ ID NO: 1-94. Also preferred is that the allelic variant is a naturally occurring allelic variant in the species of interest, particularly human.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences comprising a part of a nucleic acid sequence of the instant invention. The part may or may not encode a polypeptide, and may or may not encode a polypeptide that is a BSP. In a preferred embodiment, the part encodes a BSP. In one embodiment, the nucleic acid molecule comprises a part of a BSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that hybridizes or exhibits substantial sequence similarity to a BSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that is an allelic variant of a BSNA. In yet another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that encodes a BSP. A part comprises at least 10 nucleotides, more preferably at least 15, 17, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides. The maximum size of a nucleic acid part is one nucleotide shorter than the sequence of the nucleic acid molecule encoding the full-length protein.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences that encode fusion proteins, homologous proteins, polypeptide fragments, muteins and polypeptide analogs, as described *infra*.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences containing modifications of the native nucleic acid molecule. Examples of such modifications include, but are not limited to, nonnative internucleoside bonds, post-synthetic modifications or altered nucleotide analogues. One having ordinary skill in the art would recognize that the type of modification that may be made will depend upon the intended use of the nucleic acid molecule. For instance, when the nucleic acid molecule is

used as a hybridization probe, the range of such modifications will be limited to those that permit sequence-discriminating base pairing of the resulting nucleic acid. When used to direct expression of RNA or protein *in vitro* or *in vivo*, the range of such modifications will be limited to those that permit the nucleic acid to function properly as a 5 polymerization substrate. When the isolated nucleic acid is used as a therapeutic agent, the modifications will be limited to those that do not confer toxicity upon the isolated nucleic acid.

Accordingly, in one embodiment, a nucleic acid molecule may include nucleotide analogues that incorporate labels that are directly detectable, such as radiolabels or 10 fluorophores, or nucleotide analogues that incorporate labels that can be visualized in a subsequent reaction, such as biotin or various haptens. The labeled nucleic acid molecules are particularly useful as hybridization probes.

Common radiolabeled analogues include those labeled with  $^{33}\text{P}$ ,  $^{32}\text{P}$ , and  $^{35}\text{S}$ , such as  $\alpha$ - $^{32}\text{P}$ -dATP,  $\alpha$ - $^{32}\text{P}$ -dCTP,  $\alpha$ - $^{32}\text{P}$ -dGTP,  $\alpha$ - $^{32}\text{P}$ -dTTP,  $\alpha$ - $^{32}\text{P}$ -3'-dATP,  $\alpha$ - $^{32}\text{P}$ -ATP,  $\alpha$ - $^{32}\text{P}$ -CTP,  $\alpha$ - $^{32}\text{P}$ -GTP,  $\alpha$ - $^{32}\text{P}$ -UTP,  $\alpha$ - $^{35}\text{S}$ -dATP,  $\gamma$ - $^{35}\text{S}$ -GTP,  $\gamma$ - $^{33}\text{P}$ -dATP, and the like. 15

Commercially available fluorescent nucleotide analogues readily incorporated into the nucleic acids of the present invention include Cy3-dCTP, Cy3-dUTP, Cy5-dCTP, Cy3-dUTP (Amersham Biosciences, Piscataway, New Jersey, USA), fluorescein-12-dUTP, tetramethylrhodamine-6-dUTP, Texas Red®-5-dUTP, Cascade Blue®-7-dUTP, 20 BODIPY® FL-14-dUTP, BODIPY® TMR-14-dUTP, BODIPY® TR-14-dUTP, Rhodamine Green™-5-dUTP, Oregon Green® 488-5-dUTP, Texas Red®-12-dUTP, BODIPY® 630/650-14-dUTP, BODIPY® 650/665-14-dUTP, Alexa Fluor® 488-5-dUTP, Alexa Fluor® 532-5-dUTP, Alexa Fluor® 568-5-dUTP, Alexa Fluor® 594-5-dUTP, Alexa Fluor® 546-14-dUTP, fluorescein-12-UTP, tetramethylrhodamine-6-UTP, Texas 25 Red®-5-UTP, Cascade Blue®-7-UTP, BODIPY® FL-14-UTP, BODIPY® TMR-14-UTP, BODIPY® TR-14-UTP, Rhodamine Green™-5-UTP, Alexa Fluor® 488-5-UTP, Alexa Fluor® 546-14-UTP (Molecular Probes, Inc. Eugene, OR, USA). One may also custom synthesize nucleotides having other fluorophores. See Henegariu *et al.*, *Nature Biotechnol.* 18: 345-348 (2000).

30 Haptens that are commonly conjugated to nucleotides for subsequent labeling include biotin (biotin-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA; biotin-21-UTP, biotin-21-dUTP, Clontech Laboratories, Inc., Palo Alto, CA, USA), digoxigenin (DIG-11-dUTP, alkali labile, DIG-11-UTP, Roche Diagnostics Corp.,

Indianapolis, IN, USA), and dinitrophenyl (dinitrophenyl-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA).

Nucleic acid molecules of the present invention can be labeled by incorporation of labeled nucleotide analogues into the nucleic acid. Such analogues can be incorporated by enzymatic polymerization, such as by nick translation, random priming, polymerase chain reaction (PCR), terminal transferase tailing, and end-filling of overhangs, for DNA molecules, and *in vitro* transcription driven, e.g., from phage promoters, such as T7, T3, and SP6, for RNA molecules. Commercial kits are readily available for each such labeling approach. Analogues can also be incorporated during automated solid phase 5 chemical synthesis. Labels can also be incorporated after nucleic acid synthesis, with the 10 5' phosphate and 3' hydroxyl providing convenient sites for post-synthetic covalent attachment of detectable labels.

Other post-synthetic approaches also permit internal labeling of nucleic acids. For example, fluorophores can be attached using a cisplatin reagent that reacts with the N7 of 15 guanine residues (and, to a lesser extent, adenine bases) in DNA, RNA, and Peptide Nucleic Acids (PNA) to provide a stable coordination complex between the nucleic acid and fluorophore label (Universal Linkage System) (available from Molecular Probes, Inc., Eugene, OR, USA and Amersham Pharmacia Biotech, Piscataway, NJ, USA); *see* Alers *et al.*, *Genes, Chromosomes & Cancer* 25: 301- 305 (1999); Jelsma *et al.*, *J. NIH Res.* 5: 82 20 (1994); Van Belkum *et al.*, *BioTechniques* 16: 148-153 (1994). Alternatively, nucleic acids can be labeled using a disulfide-containing linker (FastTag<sup>TM</sup> Reagent, Vector Laboratories, Inc., Burlingame, CA, USA) that is photo- or thermally coupled to the target 25 nucleic acid using aryl azide chemistry; after reduction, a free thiol is available for coupling to a hapten, fluorophore, sugar, affinity ligand, or other marker.

One or more independent or interacting labels can be incorporated into the nucleic acid molecules of the present invention. For example, both a fluorophore and a moiety 30 that in proximity thereto acts to quench fluorescence can be included to report specific hybridization through release of fluorescence quenching or to report exonucleotidic excision. *See, e.g.*, Tyagi *et al.*, *Nature Biotechnol.* 14: 303-308 (1996); Tyagi *et al.*, *Nature Biotechnol.* 16: 49-53 (1998); Sokol *et al.*, *Proc. Natl. Acad. Sci. USA* 95: 11538-11543 (1998); Kostrikis *et al.*, *Science* 279: 1228-1229 (1998); Marras *et al.*, *Genet. Anal.* 14: 151-156 (1999); Holland *et al.*, *Proc. Natl. Acad. Sci. USA* 88: 7276-7280 (1991); Heid *et al.*, *Genome Res.* 6(10): 986-94 (1996); Kuimelis *et al.*,

*Nucleic Acids Symp. Ser.* (37): 255-6 (1997); and U.S. Patent Nos. 5,846,726, 5,925,517, 5,925,517, 5,723,591 and 5,538,848, the disclosures of which are incorporated herein by reference in their entireties.

Nucleic acid molecules of the present invention may also be modified by altering  
5 one or more native phosphodiester internucleoside bonds to more nuclease-resistant,  
internucleoside bonds. See Hartmann *et al.* (eds.), Manual of Antisense Methodology:  
Perspectives in Antisense Science, Kluwer Law International (1999); Stein *et al.* (eds.),  
Applied Antisense Oligonucleotide Technology, Wiley-Liss (1998); Chadwick *et al.*  
(eds.), Oligonucleotides as Therapeutic Agents – Symposium No. 209, John Wiley & Son  
10 Ltd (1997). Such altered internucleoside bonds are often desired for techniques or for  
targeted gene correction, Gamper *et al.*, *Nucl. Acids Res.* 28(21): 4332-4339 (2000). For  
double stranded RNA inhibition which may utilize either natural ds RNA or ds RNA  
modified in its, sugar, phosphate or base, see Hannon, *Nature* 418(11): 244-251 (2002);  
Fire *et al.* in WO 99/32619; Tuschl *et al.* in US2002/0086356; Kruetzer *et al.* in WO  
15 00/44895, the disclosures of which are incorporated herein by reference in their entirety.;  
For circular antisense, see Kool in U.S. Patent No. 5,426,180, the disclosure of which is  
incorporated herein by reference in its entirety.

Modified oligonucleotide backbones include, without limitation,  
phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters,  
20 aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene  
phosphonates and chiral phosphonates, phosphinates, phosphoramidates including  
3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates,  
thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having  
normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity  
25 wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'.  
Representative U.S. Patents that teach the preparation of the above phosphorus-containing  
linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301;  
5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131;  
5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821;  
30 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, the disclosures of  
which are incorporated herein by reference in their entireties. In a preferred embodiment,  
the modified internucleoside linkages may be used for antisense techniques.

Other modified oligonucleotide backbones do not include a phosphorus atom, but have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include  
5 those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having  
10 mixed N, O, S and CH<sub>2</sub> component parts. Representative U.S. patents that teach the preparation of the above backbones include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312;  
15 5,633,360; 5,677,437 and 5,677,439; the disclosures of which are incorporated herein by reference in their entireties.

In other preferred nucleic acid molecules, both the sugar and the internucleoside linkage are replaced with novel groups, such as peptide nucleic acids (PNA). In PNA compounds, the phosphodiester backbone of the nucleic acid is replaced with an amide-containing backbone, in particular by repeating N-(2-aminoethyl) glycine units linked by amide bonds. Nucleobases are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone, typically by methylene carbonyl linkages. PNA can be synthesized using a modified peptide synthesis protocol. PNA oligomers can be synthesized by both Fmoc and tBoc methods. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos.  
20 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference in its entirety. Automated PNA synthesis is readily achievable on commercial synthesizers (*see, e.g.*, "PNA User's Guide," Rev. 2, February 1998, Perseptive Biosystems Part No. 60138, Applied Biosystems, Inc., Foster City, CA). PNA molecules are advantageous for  
25 a number of reasons. First, because the PNA backbone is uncharged, PNA/DNA and PNA/RNA duplexes have a higher thermal stability than is found in DNA/DNA and DNA/RNA duplexes. The Tm of a PNA/DNA or PNA/RNA duplex is generally 1°C  
30 higher per base pair than the Tm of the corresponding DNA/DNA or DNA/RNA duplex

- (in 100 mM NaCl). Second, PNA molecules can also form stable PNA/DNA complexes at low ionic strength, under conditions in which DNA/DNA duplex formation does not occur. Third, PNA also demonstrates greater specificity in binding to complementary DNA because a PNA/DNA mismatch is more destabilizing than DNA/DNA mismatch. A 5 single mismatch in mixed a PNA/DNA 15-mer lowers the Tm by 8–20°C (15°C on average). In the corresponding DNA/DNA duplexes, a single mismatch lowers the Tm by 4–16°C (11°C on average). Because PNA probes can be significantly shorter than DNA probes, their specificity is greater. Fourth, PNA oligomers are resistant to degradation by enzymes, and the lifetime of these compounds is extended both *in vivo* and *in vitro*
- 10 because nucleases and proteases do not recognize the PNA polyamide backbone with nucleobase sidechains. *See, e.g., Ray et al., FASEB J.* 14(9): 1041-60 (2000); Nielsen *et al., Pharmacol Toxicol.* 86(1): 3-7 (2000); Larsen *et al., Biochim Biophys Acta.* 1489(1): 159-66 (1999); Nielsen, *Curr. Opin. Struct. Biol.* 9(3): 353-7 (1999), and Nielsen, *Curr. Opin. Biotechnol.* 10(1): 71-5 (1999).
- 15 Nucleic acid molecules may be modified compared to their native structure throughout the length of the nucleic acid molecule or can be localized to discrete portions thereof. As an example of the latter, chimeric nucleic acids can be synthesized that have discrete DNA and RNA domains and that can be used for targeted gene repair and modified PCR reactions, as further described in, Misra *et al., Biochem.* 37: 1917-1925
- 20 (1998); and Finn *et al., Nucl. Acids Res.* 24: 3357-3363 (1996), and U.S. Patent Nos. 5,760,012 and 5,731,181, the disclosures of which are incorporated herein by reference in their entireties.
- Unless otherwise specified, nucleic acid molecules of the present invention can include any topological conformation appropriate to the desired use; the term thus 25 explicitly comprehends, among others, single-stranded, double-stranded, triplexed, quadruplexed, partially double-stranded, partially-triplexed, partially-quadruplexed, branched, hairpinned, circular, and padlocked conformations. Padlock conformations and their utilities are further described in Banér *et al., Curr. Opin. Biotechnol.* 12: 11-15 (2001); Escude *et al., Proc. Natl. Acad. Sci. USA* 14: 96(19):10603-7 (1999); and Nilsson 30 *et al., Science* 265(5181): 2085-8 (1994). Triplex and quadruplex conformations, and their utilities, are reviewed in Praseuth *et al., Biochim. Biophys. Acta.* 1489(1): 181-206 (1999); Fox, *Curr. Med. Chem.* 7(1): 17-37 (2000); Kochetkova *et al., Methods Mol. Biol.*

130: 189-201 (2000); Chan *et al.*, *J. Mol. Med.* 75(4): 267-82 (1997); Rowley *et al.*, *Mol Med* 5(10): 693-700 (1999); Kool, *Annu Rev Biophys Biomol Struct.* 25: 1-28 (1996).

*Methods for Using Nucleic Acid Molecules as Probes and Primers*

5       The isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize, and quantify hybridizing nucleic acids in, and isolate hybridizing nucleic acids from, both genomic and transcript-derived nucleic acid samples. When free in solution, such probes are typically, but not invariably, detectably labeled; bound to a substrate, as in a microarray, such probes are typically, but not 10 invariably unlabeled.

In one embodiment, the isolated nucleic acid molecules of the present invention can be used as probes to detect and characterize gross alterations in the gene of a BSNA, such as deletions, insertions, translocations, and duplications of the BSNA genomic locus through fluorescence *in situ* hybridization (FISH) to chromosome spreads. *See, e.g.,* 15 Andreeff *et al.* (eds.), *Introduction to Fluorescence In Situ Hybridization: Principles and Clinical Applications*, John Wiley & Sons (1999). The isolated nucleic acid molecules of the present invention can be used as probes to assess smaller genomic alterations using, *e.g.*, Southern blot detection of restriction fragment length polymorphisms. The isolated nucleic acid molecules of the present invention can be used as probes to isolate genomic 20 clones that include a nucleic acid molecule of the present invention, which thereafter can be restriction mapped and sequenced to identify deletions, insertions, translocations, and substitutions (single nucleotide polymorphisms, SNPs) at the sequence level. Alternatively, detection techniques such as molecular beacons may be used, see Kostrikis *et al.* *Science* 279:1228-1229 (1998).

25       The isolated nucleic acid molecules of the present invention can be also be used as probes to detect, characterize, and quantify BSNA in, and isolate BSNA from, transcript-derived nucleic acid samples. In one embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by length, and quantify mRNA by Northern blot of total or poly-A<sup>+</sup>- selected RNA samples. In 30 another embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by location, and quantify mRNA by *in situ* hybridization to tissue sections. *See, e.g.,* Schwarchzacher *et al.*, *In Situ Hybridization*, Springer-Verlag New York (2000). In another preferred embodiment, the

isolated nucleic acid molecules of the present invention can be used as hybridization probes to measure the representation of clones in a cDNA library or to isolate hybridizing nucleic acid molecules acids from cDNA libraries, permitting sequence level characterization of mRNAs that hybridize to BSNA, including, without limitations, 5 identification of deletions, insertions, substitutions, truncations, alternatively spliced forms and single nucleotide polymorphisms. In yet another preferred embodiment, the nucleic acid molecules of the instant invention may be used in microarrays.

All of the aforementioned probe techniques are well within the skill in the art, and are described at greater length in standard texts such as Sambrook (2001), *supra*; Ausubel 10 (1999), *supra*; and Walker *et al.* (eds.), The Nucleic Acids Protocols Handbook, Humana Press (2000).

In another embodiment, a nucleic acid molecule of the invention may be used as a probe or primer to identify and/or amplify a second nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of the invention. In this embodiment, it is 15 preferred that the probe or primer be derived from a nucleic acid molecule encoding a BSP. More preferably, the probe or primer is derived from a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 95-156. Also preferred are probes or primers derived from a BSNA. More preferred are probes or primers derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID 20 NO: 1-94.

In general, a probe or primer is at least 10 nucleotides in length, more preferably at least 12, more preferably at least 14 and even more preferably at least 16 or 17 nucleotides in length. In an even more preferred embodiment, the probe or primer is at least 18 nucleotides in length, even more preferably at least 20 nucleotides and even more 25 preferably at least 22 nucleotides in length. Primers and probes may also be longer in length. For instance, a probe or primer may be 25 nucleotides in length, or may be 30, 40 or 50 nucleotides in length. Methods of performing nucleic acid hybridization using oligonucleotide probes are well known in the art. See, e.g., Sambrook *et al.*, 1989, *supra*, Chapter 11 and pp. 11.31-11.32 and 11.40-11.44, which describes radiolabeling of short 30 probes, and pp. 11.45-11.53, which describe hybridization conditions for oligonucleotide probes, including specific conditions for probe hybridization (pp. 11.50-11.51).

Methods of performing primer-directed amplification are also well known in the art. Methods for performing the polymerase chain reaction (PCR) are compiled, *inter alia*,

in McPherson, PCR Basics: From Background to Bench, Springer Verlag (2000); Innis *et al.* (eds.), PCR Applications: Protocols for Functional Genomics, Academic Press (1999); Gelfand *et al.* (eds.), PCR Strategies, Academic Press (1998); Newton *et al.*, PCR, Springer-Verlag New York (1997); Burke (ed.), PCR: Essential Techniques, John Wiley & Son Ltd (1996); White (ed.), PCR Cloning Protocols: From Molecular Cloning to Genetic Engineering, Vol. 67, Humana Press (1996); and McPherson *et al.* (eds.), PCR 2: A Practical Approach, Oxford University Press, Inc. (1995). Methods for performing RT-PCR are collected, *e.g.*, in Siebert *et al.* (eds.), Gene Cloning and Analysis by RT-PCR, Eaton Publishing Company/Bio Techniques Books Division, 1998; and Siebert (ed.), PCR Technique:RT-PCR, Eaton Publishing Company/ BioTechniques Books (1995).

PCR and hybridization methods may be used to identify and/or isolate nucleic acid molecules of the present invention including allelic variants, homologous nucleic acid molecules and fragments. PCR and hybridization methods may also be used to identify, amplify and/or isolate nucleic acid molecules of the present invention that encode homologous proteins, analogs, fusion protein or mureins of the invention. Nucleic acid primers as described herein can be used to prime amplification of nucleic acid molecules of the invention, using transcript-derived or genomic DNA as template.

These nucleic acid primers can also be used, for example, to prime single base extension (SBE) for SNP detection (*See, e.g.*, U.S. Pat. No. 6,004,744, the disclosure of which is incorporated herein by reference in its entirety).

Isothermal amplification approaches, such as rolling circle amplification, are also now well-described. *See, e.g.*, Schweitzer *et al.*, *Curr. Opin. Biotechnol.* 12(1): 21-7 (2001); international patent publications WO 97/19193 and WO 00/15779, and U.S. Patent Nos. 5,854,033 and 5,714,320, the disclosures of which are incorporated herein by reference in their entireties. Rolling circle amplification can be combined with other techniques to facilitate SNP detection. *See, e.g.*, Lizardi *et al.*, *Nature Genet.* 19(3): 225-32 (1998).

Nucleic acid molecules of the present invention may be bound to a substrate either covalently or noncovalently. The substrate can be porous or solid, planar or non-planar, unitary or distributed. The bound nucleic acid molecules may be used as hybridization probes, and may be labeled or unlabeled. In a preferred embodiment, the bound nucleic acid molecules are unlabeled.

In one embodiment, the nucleic acid molecule of the present invention is bound to a porous substrate, e.g., a membrane, typically comprising nitrocellulose, nylon, or positively charged derivatized nylon. The nucleic acid molecule of the present invention can be used to detect a hybridizing nucleic acid molecule that is present within a labeled 5 nucleic acid sample, e.g., a sample of transcript-derived nucleic acids. In another embodiment, the nucleic acid molecule is bound to a solid substrate, including, without limitation, glass, amorphous silicon, crystalline silicon or plastics. Examples of plastics include, without limitation, polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, 10 polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof. The solid substrate may be any shape, including rectangular, disk-like and spherical. In a preferred embodiment, the solid substrate is a microscope slide or slide-shaped substrate.

The nucleic acid molecule of the present invention can be attached covalently to a 15 surface of the support substrate or applied to a derivatized surface in a chaotropic agent that facilitates denaturation and adherence by presumed noncovalent interactions, or some combination thereof. The nucleic acid molecule of the present invention can be bound to a substrate to which a plurality of other nucleic acids are concurrently bound, hybridization to each of the plurality of bound nucleic acids being separately detectable. At low density, 20 e.g. on a porous membrane, these substrate-bound collections are typically denominated macroarrays; at higher density, typically on a solid support, such as glass, these substrate bound collections of plural nucleic acids are colloquially termed microarrays. As used herein, the term microarray includes arrays of all densities. It is, therefore, another aspect 25 of the invention to provide microarrays that comprise one or more of the nucleic acid molecules of the present invention.

In yet another embodiment, the invention is directed to single exon probes based on the BSNA disclosed herein.

*Expression Vectors, Host Cells and Recombinant Methods of Producing  
30 Polypeptides*

Another aspect of the present invention provides vectors that comprise one or more of the isolated nucleic acid molecules of the present invention, and host cells in which such vectors have been introduced.

The vectors can be used, *inter alia*, for propagating the nucleic acid molecules of the present invention in host cells (cloning vectors), for shuttling the nucleic acid molecules of the present invention between host cells derived from disparate organisms (shuttle vectors), for inserting the nucleic acid molecules of the present invention into host cell chromosomes (insertion vectors), for expressing sense or antisense RNA transcripts of the nucleic acid molecules of the present invention *in vitro* or within a host cell, and for expressing polypeptides encoded by the nucleic acid molecules of the present invention, alone or as fusion proteins with heterologous polypeptides (expression vectors). Vectors are by now well known in the art, and are described, *inter alia*, in Jones *et al.* (eds.), 5 Vectors: Cloning Applications: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Jones *et al.* (eds.), Vectors: Expression Systems: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Gacesa *et al.*, Vectors: Essential Data, John Wiley & Sons Ltd. (1995); Cid-Arregui (eds.), Viral Vectors: Basic Science and Gene Therapy, Eaton Publishing Co. (2000); Sambrook 10 (2001), *supra*; Ausubel (1999), *supra*. Furthermore, a variety of vectors are available commercially. Use of existing vectors and modifications thereof are well within the skill 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480 3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540 3545 3550 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600 3605 3610 3615 3620 3625 3630 3635 3640 3645 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695 3700 3705 3710 3715 3720 3725 3730 3735 3740 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840 3845 3850 3855 3860 3865 3870 3875 3880 3885 3890 3895 3900 3905 3910 3915 3920 3925 3930 3935 3940 3945 3950 3955 3960 3965 3970 3975 3980 3985 3990 3995 4000 4005 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4100 4105 4110 4115 4120 4125 4130 4135 4140 4145 4150 4155 4160 4165 4170 4175 4180 4185 4190 4195 4200 4205 4210 4215 4220 4225 4230 4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585 4590 4595 4600 4605 4610 4615 4620 4625 4630 4635 4640 4645 4650 4655 4660 4665 4670 4675 4680 4685 4690 4695 4700 4705 4710 4715 4720 4725 4730 4735 4740 4745 4750 4755 4760 4765 4770 4775 4780 4785 4790 4795 4800 4805 4810 4815 4820 4825 4830 4835 4840 4845 4850 4855 4860 4865 4870 4875 4880 4885 4890 4895 4900 4905 4910 4915 4920 4925 4930 4935 4940 4945 4950 4955 4960 4965 4970 4975 4980 4985 4990 4995 5000 5005 5010 5015 5020 5025 5030 5035 5040 5045 5050 5055 5060 5065 5070 5075 5080 5085 5090 5095 5100 5105 5110 5115 5120 5125 5130 5135 5140 5145 5150 5155 5160 5165 5170 5175 5180 5185 5190 5195 5200 5205 5210 5215 5220 5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 6225 6230 6235 6240 6245 6250 6255 6260 6265 6270 6275 6280 6285 6290 6295 6300 6305 6310 6315 6320 6325 6330 6335 6340 6345 6350 6355 6360 6365 6370 6375 6380 6385 6390 6395 6400 6405 6410 6415 6420 6425 6430 6435 6440 6445 6450 6455 6460 6465 6470 6475 6480 6485 6490 6495 6500 6505 6510 6515 6520 6525 6530 6535 6540 6545 6550 6555 6560 6565 6570 6575 6580 6585 6590 6595 6600 6605 6610 6615 6620 6625 6630 6635 6640 6645 6650 6655 6660 6665 6670 6675 6680 6685 6690 6695 6700 6705 6710 6715 6720 6725 6730 6735 6740 6745 6750 6755 6760 6765 6770 6775 6780 6785 6790 6795 6800 6805 6810 6815 6820 6825 6830 6835 6840 6845 6850 6855 6860 6865 6870 6875 6880 6885 6890 6895 6900 6905 6910 6915 6920 6925 6930 6935 6940 6945 6950 6955 6960 6965 6970 6975 6980 6985 6990 6995 7000 7005 7010 7015 7020 7025 7030 7035 7040 7045 7050 7055 7060 7065 7070 7075 7080 7085 7090 7095 7100 7105 7110 7115 7120 7125 7130 7135 7140 7145 7150 7155 7160 7165 7170 7175 7180 7185 7190 7195 7200 7205 7210 7215 7220 7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 8225 8230 8235 8240 8245 8250 8255 8260 8265 8270 8275 8280 8285 8290 8295 8300 8305 8310 8315 8320 8325 8330 8335 8340 8345 8350 8355 8360 8365 8370 8375 8380 8385 8390 8395 8400 8405 8410 8415 8420 8425 8430 8435 8440 8445 8450 8455 8460 8465 8470 8475 8480 8485 8490 8495 8500 8505 8510 8515 8520 8525 8530 8535 8540 8545 8550 8555 8560 8565 8570 8575 8580 8585 8590 8595 8600 8605 8610 8615 8620 8625 8630 8635 8640 8645 8650 8655 8660 8665 8670 8675 8680 8685 8690 8695 8700 8705 8710 8715 8720 8725 8730 8735 8740 8745 8750 8755 8760 8765 8770 8775 8780 8785 8790 8795 8800 8805 8810 8815 8820 8825 8830 8835 8840 8845 8850 8855 8860 8865 8870 8875 8880 8885 8890 8895 8900 8905 8910 8915 8920 8925 8930 8935 8940 8945 8950 8955 8960 8965 8970 8975 8980 8985 8990 8995 9000 9005 9010 9015 9020 9025 9030 9035 9040 9045 9050 9055 9060 9065 9070 9075 9080 9085 9090 9095 9100 9105 9110 9115 9120 9125 9130 9135 9140 9145 9150 9155 9160 9165 9170 9175 9180 9185 9190 9195 9200 9205 9210 9215 9220 9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775 9780 9785 9790 9795 9800 9805 9810 9815 9820 9825 9830 9835 9840 9845 9850 9855 9860 9865 9870 9875 9880 9885 9890 9895 9900 9905 9910 9915 9920 9925 9930 9935 9940 9945 9950 9955 9960 9965 9970 9975 9980 9985 9990 9995 9999 10000 10005 10010 10015 10020 10025 10030 10035 10040 10045 10050 10055 10060 10065 10070 10075 10080 10085 10090 10095 100100 100105 100110 100115 100120 100125 100130 100135 100140 100145 100150 100155 100160 100165 100170 100175 100180 100185 100190 100195 100200 100205 100210 100215 100220 100225 100230 100235 100240 100245 100250 100255 100260 100265 100270 100275 100280 100285 100290 100295 100300 100305 100310 100315 100320 100325 100330 100335 100340 100345 100350 100355 100360 100365 100370 100375 100380 100385 100390 100395 100400 100405 100410 100415 100420 100425 100430 100435 100440 100445 100450 100455 100460 100465 100470 100475 100480 100485 100490 100495 100500 100505 100510 100515 100520 100525 100530 100535 100540 100545 100550 100555 100560 100565 100570 100575 100580 100585 100590 100595 100600 100605 100610 100615 100620 100625 100630 100635 100640 100645 100650 100655 100660 100665 100670 100675 100680 100685 100690 100695 100700 100705 100710 100715 100720 100725 100730 100735 100740 100745 100750 100755 100760 100765 100770 100775 100780 100

nucleic acid molecules of the instant invention. Useful expression vectors for bacterial hosts include bacterial plasmids, such as those from *E. coli*, *Bacillus* or *Streptomyces*, including pBluescript, pGEX-2T, pUC vectors, col E1, pCR1, pBR322, pMB9 and their derivatives, wider host range plasmids, such as RP4, phage DNAs, e.g., the numerous 5 derivatives of phage lambda, e.g., NM989, λGT10 and λGT11, and other phages, e.g., M13 and filamentous single stranded phage DNA. Where *E. coli* is used as host, selectable markers are, analogously, chosen for selectivity in gram negative bacteria: e.g., typical markers confer resistance to antibiotics, such as ampicillin, tetracycline, chloramphenicol, kanamycin, streptomycin and zeocin; auxotrophic markers can also be 10 used.

In other embodiments, eukaryotic host cells, such as yeast, insect, mammalian or plant cells, may be used. Yeast cells, typically *S. cerevisiae*, are useful for eukaryotic genetic studies, due to the ease of targeting genetic changes by homologous recombination and the ability to easily complement genetic defects using recombinantly expressed 15 proteins. Yeast cells are useful for identifying interacting protein components, e.g. through use of a two-hybrid system. In a preferred embodiment, yeast cells are useful for protein expression. Vectors of the present invention for use in yeast will typically, but not invariably, contain an origin of replication suitable for use in yeast and a selectable marker that is functional in yeast. Yeast vectors include Yeast Integrating plasmids (e.g., YIp5) 20 and Yeast Replicating plasmids (the YRp and YEp series plasmids), Yeast Centromere plasmids (the YCp series plasmids), Yeast Artificial Chromosomes (YACs) which are based on yeast linear plasmids, denoted YLp, pGPD-2, 2μ plasmids and derivatives thereof, and improved shuttle vectors such as those described in Gietz *et al.*, *Gene*, 74: 25 527-34 (1988) (YIplac, YEplac and YCplac). Selectable markers in yeast vectors include a variety of auxotrophic markers, the most common of which are (in *Saccharomyces cerevisiae*) URA3, HIS3, LEU2, TRP1 and LYS2, which complement specific auxotrophic mutations, such as ura3-52, his3-D1, leu2-D1, trp1-D1 and lys2-201.

Insect cells may be chosen for high efficiency protein expression. Where the host 30 cells are from *Spodoptera frugiperda*, e.g., Sf9 and Sf21 cell lines, and expressSFTM cells (Protein Sciences Corp., Meriden, CT, USA), the vector replicative strategy is typically based upon the baculovirus life cycle. Typically, baculovirus transfer vectors are used to replace the wild-type AcMNPV polyhedrin gene with a heterologous gene of interest. Sequences that flank the polyhedrin gene in the wild-type genome are positioned 5' and 3'

of the expression cassette on the transfer vectors. Following co-transfection with AcMNPV DNA, a homologous recombination event occurs between these sequences resulting in a recombinant virus carrying the gene of interest and the polyhedrin or p10 promoter. Selection can be based upon visual screening for lacZ fusion activity.

5       The host cells may also be mammalian cells, which are particularly useful for expression of proteins intended as pharmaceutical agents, and for screening of potential agonists and antagonists of a protein or a physiological pathway. Mammalian vectors intended for autonomous extrachromosomal replication will typically include a viral origin, such as the SV40 origin (for replication in cell lines expressing the large T-antigen, 10 such as COS1 and COS7 cells), the papillomavirus origin, or the EBV origin for long term episomal replication (for use, *e.g.*, in 293-EBNA cells, which constitutively express the EBV EBNA-1 gene product and adenovirus E1A). Vectors intended for integration, and thus replication as part of the mammalian chromosome, can, but need not, include an origin of replication functional in mammalian cells, such as the SV40 origin. Vectors 15 based upon viruses, such as adenovirus, adeno-associated virus, vaccinia virus, and various mammalian retroviruses, will typically replicate according to the viral replicative strategy. Selectable markers for use in mammalian cells include, include but are not limited to, resistance to neomycin (G418), blasticidin, hygromycin and zeocin, and selection based upon the purine salvage pathway using HAT medium.

20       Expression in mammalian cells can be achieved using a variety of plasmids, including pSV2, pBC12BI, and p91023, as well as lytic virus vectors (*e.g.*, vaccinia virus, adeno virus, and baculovirus), episomal virus vectors (*e.g.*, bovine papillomavirus), and retroviral vectors (*e.g.*, murine retroviruses). Useful vectors for insect cells include baculoviral vectors and pVL 941.

25       Plant cells can also be used for expression, with the vector replicon typically derived from a plant virus (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) and selectable markers chosen for suitability in plants.

30       It is known that codon usage of different host cells may be different. For example, a plant cell and a human cell may exhibit a difference in codon preference for encoding a particular amino acid. As a result, human mRNA may not be efficiently translated in a plant, bacteria or insect host cell. Therefore, another embodiment of this invention is directed to codon optimization. The codons of the nucleic acid molecules of the invention

may be modified to resemble, as much as possible, genes naturally contained within the host cell without altering the amino acid sequence encoded by the nucleic acid molecule.

Any of a wide variety of expression control sequences may be used in these vectors to express the nucleic acid molecules of this invention. Such useful expression control sequences include the expression control sequences associated with structural genes of the foregoing expression vectors. Expression control sequences that control transcription include, e.g., promoters, enhancers and transcription termination sites. Expression control sequences in eukaryotic cells that control post-transcriptional events include splice donor and acceptor sites and sequences that modify the half-life of the transcribed RNA, e.g., sequences that direct poly(A) addition or binding sites for RNA-binding proteins. Expression control sequences that control translation include ribosome binding sites, sequences which direct targeted expression of the polypeptide to or within particular cellular compartments, and sequences in the 5' and 3' untranslated regions that modify the rate or efficiency of translation.

Examples of useful expression control sequences for a prokaryote, e.g., *E. coli*, will include a promoter, often a phage promoter, such as phage lambda pL promoter, the trc promoter, a hybrid derived from the trp and lac promoters, the bacteriophage T7 promoter (in *E. coli* cells engineered to express the T7 polymerase), the TAC or TRC system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, and the araBAD operon. Prokaryotic expression vectors may further include transcription terminators, such as the aspA terminator, and elements that facilitate translation, such as a consensus ribosome binding site and translation termination codon, Schomer *et al.*, *Proc. Natl. Acad. Sci. USA* 83: 8506-8510 (1986).

Expression control sequences for yeast cells, typically *S. cerevisiae*, will include a yeast promoter, such as the CYC1 promoter, the GAL1 promoter, the GAL10 promoter, ADH1 promoter, the promoters of the yeast  $\alpha$ -mating system, or the GPD promoter, and will typically have elements that facilitate transcription termination, such as the transcription termination signals from the CYC1 or ADH1 gene.

Expression vectors useful for expressing proteins in mammalian cells will include a promoter active in mammalian cells. These promoters include, but are not limited to, those derived from mammalian viruses, such as the enhancer-promoter sequences from the immediate early gene of the human cytomegalovirus (CMV), the enhancer-promoter sequences from the Rous sarcoma virus long terminal repeat (RSV LTR), the enhancer-

promoter from SV40 and the early and late promoters of adenovirus. Other expression control sequences include the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase. Other expression control sequences include those from the gene comprising the BSNA of interest. Often, expression is enhanced by 5 incorporation of polyadenylation sites, such as the late SV40 polyadenylation site and the polyadenylation signal and transcription termination sequences from the bovine growth hormone (BGH) gene, and ribosome binding sites. Furthermore, vectors can include introns, such as intron II of rabbit  $\beta$ -globin gene and the SV40 splice elements.

Preferred nucleic acid vectors also include a selectable or amplifiable marker gene 10 and means for amplifying the copy number of the gene of interest. Such marker genes are well known in the art. Nucleic acid vectors may also comprise stabilizing sequences (e.g., ori- or ARS-like sequences and telomere-like sequences), or may alternatively be designed to favor directed or non-directed integration into the host cell genome. In a preferred embodiment, nucleic acid sequences of this invention are inserted in frame into an 15 expression vector that allows a high level expression of an RNA that encodes a protein comprising the encoded nucleic acid sequence of interest. Nucleic acid cloning and sequencing methods are well known to those of skill in the art and are described in an assortment of laboratory manuals, including Sambrook (1989), *supra*, Sambrook (2000), *supra*; and Ausubel (1992), *supra*, Ausubel (1999), *supra*. Product information from 20 manufacturers of biological, chemical and immunological reagents also provide useful information.

Expression vectors may be either constitutive or inducible. Inducible vectors include either naturally inducible promoters, such as the trc promoter, which is regulated by the lac operon, and the pL promoter, which is regulated by tryptophan, the 25 MMTV-LTR promoter, which is inducible by dexamethasone, or can contain synthetic promoters and/or additional elements that confer inducible control on adjacent promoters. Examples of inducible synthetic promoters are the hybrid P<sub>lac</sub>/ara-1 promoter and the PLtetO-1 promoter. The PLtetO-1 promoter takes advantage of the high expression levels from the PL promoter of phage lambda, but replaces the lambda repressor sites with two 30 copies of operator 2 of the Tn10 tetracycline resistance operon, causing this promoter to be tightly repressed by the Tet repressor protein and induced in response to tetracycline (Tc) and Tc derivatives such as anhydrotetracycline. Vectors may also be inducible because they contain hormone response elements, such as the glucocorticoid response

element (GRE) and the estrogen response element (ERE), which can confer hormone inducibility where vectors are used for expression in cells having the respective hormone receptors. To reduce background levels of expression, elements responsive to ecdysone, an insect hormone, can be used instead, with coexpression of the ecdysone receptor.

5 In one embodiment of the invention, expression vectors can be designed to fuse the expressed polypeptide to small protein tags that facilitate purification and/or visualization. Such tags include a polyhistidine tag that facilitates purification of the fusion protein by immobilized metal affinity chromatography, for example using NiNTA resin (Qiagen Inc., Valencia, CA, USA) or TALON™ resin (cobalt immobilized affinity chromatography

10 medium, Clontech Labs, Palo Alto, CA, USA). The fusion protein can include a chitin-binding tag and self-excising intein, permitting chitin-based purification with self-removal of the fused tag (IMPACT™ system, New England Biolabs, Inc., Beverley, MA, USA). Alternatively, the fusion protein can include a calmodulin-binding peptide tag, permitting purification by calmodulin affinity resin (Stratagene, La Jolla, CA, USA), or a specifically

15 excisable fragment of the biotin carboxylase carrier protein, permitting purification of *in vivo* biotinylated protein using an avidin resin and subsequent tag removal (Promega, Madison, WI, USA). As another useful alternative, the polypeptides of the present invention can be expressed as a fusion to glutathione-S-transferase, the affinity and specificity of binding to glutathione permitting purification using glutathione affinity

20 resins, such as Glutathione-Superflow Resin (Clontech Laboratories, Palo Alto, CA, USA), with subsequent elution with free glutathione. Other tags include, for example, the Xpress epitope, detectable by anti-Xpress antibody (Invitrogen, Carlsbad, CA, USA), a myc tag, detectable by anti-myc tag antibody, the V5 epitope, detectable by anti-V5 antibody (Invitrogen, Carlsbad, CA, USA), FLAG® epitope, detectable by anti-FLAG®

25 antibody (Stratagene, La Jolla, CA, USA), and the HA epitope, detectable by anti-HA antibody.

For secretion of expressed polypeptides, vectors can include appropriate sequences that encode secretion signals, such as leader peptides. For example, the pSecTag2 vectors (Invitrogen, Carlsbad, CA, USA) are 5.2 kb mammalian expression vectors that carry the

30 secretion signal from the V-J2-C region of the mouse Ig kappa-chain for efficient secretion of recombinant proteins from a variety of mammalian cell lines.

Expression vectors can also be designed to fuse proteins encoded by the heterologous nucleic acid insert to polypeptides that are larger than purification and/or

identification tags. Useful protein fusions include those that permit display of the encoded protein on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, such as those that have a green fluorescent protein (GFP)-like chromophore, fusions to the IgG Fc region, and fusions for use in two hybrid systems.

5 Vectors for phage display fuse the encoded polypeptide to, e.g., the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13. See Barbas *et al.*, Phage Display: A Laboratory Manual, Cold Spring Harbor Laboratory Press (2001); Kay *et al.* (eds.), Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press, Inc., (1996); Abelson *et al.* (eds.), Combinatorial Chemistry (Methods in Enzymology, Vol. 267) Academic Press (1996). Vectors for yeast display, e.g. the pYD1 yeast display vector (Invitrogen, Carlsbad, CA, USA), use the α-agglutinin yeast adhesion receptor to display recombinant protein on the surface of *S. cerevisiae*. Vectors for mammalian display, e.g., the pDisplay™ vector (Invitrogen, Carlsbad, CA, USA), target recombinant proteins using an N-terminal cell surface targeting signal and a C-terminal transmembrane anchoring domain of platelet derived growth factor receptor.

10

15

A wide variety of vectors now exist that fuse proteins encoded by heterologous nucleic acids to the chromophore of the substrate-independent, intrinsically fluorescent green fluorescent protein from *Aequorea victoria* ("GFP") and its variants. The GFP-like chromophore can be selected from GFP-like chromophores found in naturally occurring proteins, such as *A. victoria* GFP (GenBank accession number AAA27721), *Renilla reniformis* GFP, FP583 (GenBank accession no. AF168419) (DsRed), FP593 (AF272711), FP483 (AF168420), FP484 (AF168424), FP595 (AF246709), FP486 (AF168421), FP538 (AF168423), and FP506 (AF168422), and need include only so much of the native protein as is needed to retain the chromophore's intrinsic fluorescence. Methods for determining the minimal domain required for fluorescence are known in the art. See Li *et al.*, *J. Biol. Chem.* 272: 28545-28549 (1997). Alternatively, the GFP-like chromophore can be selected from GFP-like chromophores modified from those found in nature. The methods for engineering such modified GFP-like chromophores and testing them for fluorescence activity, both alone and as part of protein fusions, are well known in the art. See Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Palm *et al.*, *Methods Enzymol.* 302: 378-394 (1999). A variety of such modified chromophores are now commercially available and can readily be used in the fusion proteins of the present invention. These include EGFP ("enhanced

20

25

30

GFP”), EBFP (“enhanced blue fluorescent protein”), BFP2, EYFP (“enhanced yellow fluorescent protein”), ECFP (“enhanced cyan fluorescent protein”) or Citrine. EGFP (*see, e.g.*, Cormack *et al.*, *Gene* 173: 33–38 (1996); U.S. Patent Nos. 6,090,919 and 5,804,387, the disclosures of which are incorporated herein by reference in their entireties) is found on a variety of vectors, both plasmid and viral, which are available commercially (Clontech Labs, Palo Alto, CA, USA); EBFP is optimized for expression in mammalian cells whereas BFP2, which retains the original jellyfish codons, can be expressed in bacteria (*see, e.g.*, Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Cormack *et al.*, *Gene* 173: 33-38 (1996)). Vectors containing these blue-shifted variants are available from 5 Clontech Labs (Palo Alto, CA, USA). Vectors containing EYFP, ECFP (*see, e.g.*, Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996); Miyawaki *et al.*, *Nature* 388: 882-887 (1997)) and Citrine (*see, e.g.*, Heikal *et al.*, *Proc. Natl. Acad. Sci. USA* 97: 11996-12001 (2000)) are also available from Clontech Labs. The GFP-like chromophore can also be drawn from other modified GFPs, including those described in U.S. Patent Nos. 6,124,128; 6,096,865; 10 15 6,090,919; 6,066,476; 6,054,321; 6,027,881; 5,968,750; 5,874,304; 5,804,387; 5,777,079; 5,741,668; and 5,625,048, the disclosures of which are incorporated herein by reference in their entireties. *See also* Conn (ed.), Green Fluorescent Protein (Methods in Enzymology, Vol. 302), Academic Press, Inc. (1999); Yang, *et al.*, *J Biol Chem*, 273: 8212-6 (1998); Bevis *et al.*, *Nature Biotechnology*, 20:83-7 (2002). The GFP-like chromophore of each 20 25 of these GFP variants can usefully be included in the fusion proteins of the present invention.

Fusions to the IgG Fc region increase serum half-life of protein pharmaceutical products through interaction with the FcRn receptor (also denominated the FcRp receptor and the Brambell receptor, FcRb), further described in International Patent Application nos. WO 97/43316, WO 97/34631, WO 96/32478, WO 96/18412, the disclosures of which 25 are incorporated herein by reference in their entireties.

For long-term, high-yield recombinant production of the polypeptides of the present invention, stable expression is preferred. Stable expression is readily achieved by integration into the host cell genome of vectors having selectable markers, followed by 30 selection of these integrants. Vectors such as pUB6/V5-His A, B, and C (Invitrogen, Carlsbad, CA, USA) are designed for high-level stable expression of heterologous proteins in a wide range of mammalian tissue types and cell lines. pUB6/V5-His uses the promoter/enhancer sequence from the human ubiquitin C gene to drive expression of

recombinant proteins: expression levels in 293, CHO, and NIH3T3 cells are comparable to levels from the CMV and human EF-1 $\alpha$  promoters. The bsd gene permits rapid selection of stably transfected mammalian cells with the potent antibiotic blasticidin.

Replication incompetent retroviral vectors, typically derived from Moloney murine leukemia virus, also are useful for creating stable transfectants having integrated provirus. The highly efficient transduction machinery of retroviruses, coupled with the availability of a variety of packaging cell lines such as RetroPack<sup>TM</sup> PT 67, EcoPack2<sup>TM</sup>-293, AmphiPack-293, and GP2-293 cell lines (all available from Clontech Laboratories, Palo Alto, CA, USA) allow a wide host range to be infected with high efficiency; varying the multiplicity of infection readily adjusts the copy number of the integrated provirus.

Of course, not all vectors and expression control sequences will function equally well to express the nucleic acid molecules of this invention. Neither will all hosts function equally well with the same expression system. However, one of skill in the art may make a selection among these vectors, expression control sequences and hosts without undue experimentation and without departing from the scope of this invention. For example, in selecting a vector, the host must be considered because the vector must be replicated in it. The vector's copy number, the ability to control that copy number, the ability to control integration, if any, and the expression of any other proteins encoded by the vector, such as antibiotic or other selection markers, should also be considered. The present invention further includes host cells comprising the vectors of the present invention, either present episomally within the cell or integrated, in whole or in part, into the host cell chromosome. Among other considerations, some of which are described above, a host cell strain may be chosen for its ability to process the expressed polypeptide in the desired fashion. Such post-translational modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation, and it is an aspect of the present invention to provide BSPs with such post-translational modifications.

In selecting an expression control sequence, a variety of factors should also be considered. These include, for example, the relative strength of the sequence, its controllability, and its compatibility with the nucleic acid molecules of this invention, particularly with regard to potential secondary structures. Unicellular hosts should be selected by consideration of their compatibility with the chosen vector, the toxicity of the product coded for by the nucleic acid sequences of this invention, their secretion

characteristics, their ability to fold the polypeptide correctly, their fermentation or culture requirements, and the ease of purification from them of the products coded for by the nucleic acid molecules of this invention.

The recombinant nucleic acid molecules and more particularly, the expression vectors of this invention may be used to express the polypeptides of this invention as recombinant polypeptides in a heterologous host cell. The polypeptides of this invention may be full-length or less than full-length polypeptide fragments recombinantly expressed from the nucleic acid molecules according to this invention. Such polypeptides include analogs, derivatives and muteins that may or may not have biological activity.

Vectors of the present invention will also often include elements that permit *in vitro* transcription of RNA from the inserted heterologous nucleic acid. Such vectors typically include a phage promoter, such as that from T7, T3, or SP6, flanking the nucleic acid insert. Often two different such promoters flank the inserted nucleic acid, permitting separate *in vitro* production of both sense and antisense strands.

Transformation and other methods of introducing nucleic acids into a host cell (*e.g.*, conjugation, protoplast transformation or fusion, transfection, electroporation, liposome delivery, membrane fusion techniques, high velocity DNA-coated pellets, viral infection and protoplast fusion) can be accomplished by a variety of methods that are well known in the art (*See, for instance, Ausubel, supra, and Sambrook et al., supra*).

Bacterial, yeast, plant or mammalian cells are transformed or transfected with an expression vector, such as a plasmid, a cosmid, or the like, wherein the expression vector comprises the nucleic acid of interest. Alternatively, the cells may be infected by a viral expression vector comprising the nucleic acid of interest. Depending upon the host cell, vector, and method of transformation used, transient or stable expression of the polypeptide will be constitutive or inducible. One having ordinary skill in the art will be able to decide whether to express a polypeptide transiently or stably, and whether to express the protein constitutively or inducibly.

A wide variety of unicellular host cells are useful in expressing the DNA sequences of this invention. These hosts may include well known eukaryotic and prokaryotic hosts, such as strains of, fungi, yeast, insect cells such as *Spodoptera frugiperda* (SF9), animal cells such as CHO, as well as plant cells in tissue culture. Representative examples of appropriate host cells include, but are not limited to, bacterial cells, such as *E. coli*, *Caulobacter crescentus*, *Streptomyces* species, and *Salmonella*

*typhimurium*; yeast cells, such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Pichia pastoris*, *Pichia methanolica*; insect cell lines, such as those from *Spodoptera frugiperda* — e.g., Sf9 and Sf21 cell lines, and expresSF™ cells (Protein Sciences Corp., Meriden, CT, USA) — *Drosophila* S2 cells, and *Trichoplusia ni* High Five® Cells (Invitrogen, Carlsbad, CA, USA); and mammalian cells. Typical mammalian cells include BHK cells, BSC 1 cells, BSC 40 cells, BMT 10 cells, VERO cells, COS1 cells, COS7 cells, Chinese hamster ovary (CHO) cells, 3T3 cells, NIH 3T3 cells, 293 cells, HEPG2 cells, HeLa cells, L cells, MDCK cells, HEK293 cells, WI38 cells, murine ES cell lines (e.g., from strains 129/SV, C57/BL6, DBA-1, 129/SVJ), K562 cells, Jurkat cells, and BW5147 cells. Other mammalian cell lines are well known and readily available from the American Type Culture Collection (ATCC) (Manassas, VA, USA) and the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the Coriell Cell Repositories (Camden, NJ, USA). Cells or cell lines derived from breast are particularly preferred because they may provide a more native post-translational processing. Particularly preferred are human breast cells.

Particular details of the transfection, expression and purification of recombinant proteins are well documented and are understood by those of skill in the art. Further details on the various technical aspects of each of the steps used in recombinant production of foreign genes in bacterial cell expression systems can be found in a number of texts and laboratory manuals in the art. See, e.g., Ausubel (1992), *supra*, Ausubel (1999), *supra*, Sambrook (1989), *supra*, and Sambrook (2001), *supra*.

Methods for introducing the vectors and nucleic acid molecules of the present invention into the host cells are well known in the art; the choice of technique will depend primarily upon the specific vector to be introduced and the host cell chosen.

Nucleic acid molecules and vectors may be introduced into prokaryotes, such as *E. coli*, in a number of ways. For instance, phage lambda vectors will typically be packaged using a packaging extract (e.g., Gigapack® packaging extract, Stratagene, La Jolla, CA, USA), and the packaged virus used to infect *E. coli*.

Plasmid vectors will typically be introduced into chemically competent or electrocompetent bacterial cells. *E. coli* cells can be rendered chemically competent by treatment, e.g., with CaCl<sub>2</sub>, or a solution of Mg<sup>2+</sup>, Mn<sup>2+</sup>, Ca<sup>2+</sup>, Rb<sup>+</sup> or K<sup>+</sup>, dimethyl sulfoxide, dithiothreitol, and hexamine cobalt (III), Hanahan, *J. Mol. Biol.* 166(4):557-80 (1983), and vectors introduced by heat shock. A wide variety of chemically competent

strains are also available commercially (e.g., Epicurian Coli® XL10-Gold® Ultracompetent Cells (Stratagene, La Jolla, CA, USA); DH5 $\alpha$  competent cells (Clontech Laboratories, Palo Alto, CA, USA); and TOP10 Chemically Competent E. coli Kit (Invitrogen, Carlsbad, CA, USA)). Bacterial cells can be rendered electrocompetent to 5 take up exogenous DNA by electroporation by various pre-pulse treatments; vectors are introduced by electroporation followed by subsequent outgrowth in selected media. An extensive series of protocols is provided by BioRad (Richmond, CA, USA).

Vectors can be introduced into yeast cells by spheroplasting, treatment with lithium salts, electroporation, or protoplast fusion. Spheroplasts are prepared by the action 10 of hydrolytic enzymes such as a snail-gut extract, usually denoted Glusulase or Zymolyase, or an enzyme from *Arthrobacter luteus* to remove portions of the cell wall in the presence of osmotic stabilizers, typically 1 M sorbitol. DNA is added to the spheroplasts, and the mixture is co-precipitated with a solution of polyethylene glycol (PEG) and Ca<sup>2+</sup>. Subsequently, the cells are resuspended in a solution of sorbitol, mixed 15 with molten agar and then layered on the surface of a selective plate containing sorbitol.

For lithium-mediated transformation, yeast cells are treated with lithium acetate to permeabilize the cell wall, DNA is added and the cells are co-precipitated with PEG. The cells are exposed to a brief heat shock, washed free of PEG and lithium acetate, and subsequently spread on plates containing ordinary selective medium. Increased 20 frequencies of transformation are obtained by using specially-prepared single-stranded carrier DNA and certain organic solvents. Schiestl *et al.*, *Curr. Genet.* 16(5-6): 339-46 (1989).

For electroporation, freshly-grown yeast cultures are typically washed, suspended 25 in an osmotic protectant, such as sorbitol, mixed with DNA, and the cell suspension pulsed in an electroporation device. Subsequently, the cells are spread on the surface of plates containing selective media. Becker *et al.*, *Methods Enzymol.* 194: 182-187 (1991). The efficiency of transformation by electroporation can be increased over 100-fold by using PEG, single-stranded carrier DNA and cells that are in late log-phase of growth. Larger constructs, such as YACs, can be introduced by protoplast fusion.

30 Mammalian and insect cells can be directly infected by packaged viral vectors, or transfected by chemical or electrical means. For chemical transfection, DNA can be coprecipitated with CaPO<sub>4</sub> or introduced using liposomal and nonliposomal lipid-based agents. Commercial kits are available for CaPO<sub>4</sub> transfection (CalPhos™ Mammalian

Transfection Kit, Clontech Laboratories, Palo Alto, CA, USA), and lipid-mediated transfection can be practiced using commercial reagents, such as LIPOFECTAMINE™ 2000, LIPOFECTAMINE™ Reagent, CELLFECTIN® Reagent, and LIPOFECTIN® Reagent (Invitrogen, Carlsbad, CA, USA), DOTAP Liposomal Transfection Reagent, 5 FuGENE 6, X-tremeGENE Q2, DOSPER, (Roche Molecular Biochemicals, Indianapolis, IN USA), Effectene™, PolyFect®, Superfect® (Qiagen, Inc., Valencia, CA, USA). Protocols for electroporating mammalian cells can be found in, for example, ; Norton *et al.* (eds.), Gene Transfer Methods: Introducing DNA into Living Cells and Organisms, BioTechniques Books, Eaton Publishing Co. (2000). Other transfection techniques 10 include transfection by particle bombardment and microinjection. See, e.g., Cheng *et al.*, *Proc. Natl. Acad. Sci. USA* 90(10): 4455-9 (1993); Yang *et al.*, *Proc. Natl. Acad. Sci. USA* 87(24): 9568-72 (1990).

Production of the recombinantly produced proteins of the present invention can optionally be followed by purification.

15 Purification of recombinantly expressed proteins is now well within the skill in the art and thus need not be detailed here. See, e.g., Thorner *et al.* (eds.), Applications of Chimeric Genes and Hybrid Proteins, Part A: Gene Expression and Protein Purification (Methods in Enzymology, Vol. 326), Academic Press (2000); Harbin (ed.), Cloning, Gene Expression and Protein Purification : Experimental Procedures and Process Rationale, 20 Oxford Univ. Press (2001); Marshak *et al.*, Strategies for Protein Purification and Characterization: A Laboratory Course Manual, Cold Spring Harbor Laboratory Press (1996); and Roe (ed.), Protein Purification Applications, Oxford University Press (2001).

Briefly, however, if purification tags have been fused through use of an expression vector that appends such tag, purification can be effected, at least in part, by means 25 appropriate to the tag, such as use of immobilized metal affinity chromatography for polyhistidine tags. Other techniques common in the art include ammonium sulfate fractionation, immunoprecipitation, fast protein liquid chromatography (FPLC), high performance liquid chromatography (HPLC), and preparative gel electrophoresis.

30 Polypeptides, including Fragments Muteins, Homologous Proteins, Allelic Variants, Analogs and Derivatives

Another aspect of the invention relates to polypeptides encoded by the nucleic acid molecules described herein. In a preferred embodiment, the polypeptide is a breast

specific polypeptide (BSP). In an even more preferred embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO:95-156 or is derived from a polypeptide having the amino acid sequence of SEQ ID NO: 95-156. A polypeptide as defined herein may be produced recombinantly, as discussed *supra*, may be isolated from a cell that 5 naturally expresses the protein, or may be chemically synthesized following the teachings of the specification and using methods well known to those having ordinary skill in the art.

Polypeptides of the present invention may also comprise a part or fragment of a BSP. In a preferred embodiment, the fragment is derived from a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 95-156.

10 Polypeptides of the present invention comprising a part or fragment of an entire BSP may or may not be BSPs. For example, a full-length polypeptide may be breast-specific, while a fragment thereof may be found in other tissues as well as in breast. A polypeptide that is not a BSP, whether it is a fragment, analog, mutein, homologous protein or derivative, is nevertheless useful, especially for immunizing animals to prepare anti-BSP antibodies. In 15 a preferred embodiment, the part or fragment is a BSP. Methods of determining whether a polypeptide of the present invention is a BSP are described *infra*.

Polypeptides of the present invention comprising fragments of at least 6 contiguous amino acids are also useful in mapping B cell and T cell epitopes of the reference protein. See, e.g., Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81: 3998-4002 20 and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. Because the fragment need not itself be immunogenic, part of an immunodominant epitope, nor even recognized by native antibody, to be useful in such epitope mapping, all fragments of at least 6 amino acids of a polypeptide of the present invention have utility in such a study.

25 Polypeptides of the present invention comprising fragments of at least 8 contiguous amino acids, often at least 15 contiguous amino acids, are useful as immunogens for raising antibodies that recognize polypeptides of the present invention. See, e.g., Lerner, *Nature* 299: 592-596 (1982); Shinnick *et al.*, *Annu. Rev. Microbiol.* 37: 425-46 (1983); Sutcliffe *et al.*, *Science* 219: 660-6 (1983). As further described in the 30 above-cited references, virtually all 8-mers, conjugated to a carrier, such as a protein, prove immunogenic and are capable of eliciting antibody for the conjugated peptide; accordingly, all fragments of at least 8 amino acids of the polypeptides of the present invention have utility as immunogens.

Polypeptides comprising fragments of at least 8, 9, 10 or 12 contiguous amino acids are also useful as competitive inhibitors of binding of the entire polypeptide, or a portion thereof, to antibodies (as in epitope mapping), and to natural binding partners, such as subunits in a multimeric complex or to receptors or ligands of the subject protein; 5 this competitive inhibition permits identification and separation of molecules that bind specifically to the polypeptide of interest. See U.S. Patent Nos. 5,539,084 and 5,783,674, incorporated herein by reference in their entireties.

The polypeptide of the present invention thus preferably is at least 6 amino acids in length, typically at least 8, 9, 10 or 12 amino acids in length, and often at least 15 amino 10 acids in length. Often, the polypeptide of the present invention is at least 20 amino acids in length, even 25 amino acids, 30 amino acids, 35 amino acids, or 50 amino acids or more in length. Of course, larger polypeptides having at least 75 amino acids, 100 amino acids, or even 150 amino acids are also useful, and at times preferred.

One having ordinary skill in the art can produce fragments by truncating the 15 nucleic acid molecule, e.g., a BSNA, encoding the polypeptide and then expressing it recombinantly. Alternatively, one can produce a fragment by chemically synthesizing a portion of the full-length polypeptide. One may also produce a fragment by enzymatically cleaving either a recombinant polypeptide or an isolated naturally occurring polypeptide. Methods of producing polypeptide fragments are well known in the art. *See, e.g.,* 20 Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. In one embodiment, a polypeptide comprising only a fragment, preferably a fragment of a BSP, may be produced by chemical or enzymatic cleavage of a BSP polypeptide. In a preferred embodiment, a polypeptide fragment is produced by expressing a nucleic acid molecule of the present invention encoding a fragment, 25 preferably of a BSP, in a host cell.

Polypeptides of the present invention are also inclusive of mutants, fusion proteins, homologous proteins and allelic variants.

A mutant protein, or mutein, may have the same or different properties compared to a naturally occurring polypeptide and comprises at least one amino acid insertion, 30 duplication, deletion, rearrangement or substitution compared to the amino acid sequence of a native polypeptide. Small deletions and insertions can often be found that do not alter the function of a protein. Muteins may or may not be breast-specific. Preferably, the mutein is breast-specific. More preferably the mutein is a polypeptide that comprises at

least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of SEQ ID NO: 95-156. Accordingly, in a preferred embodiment, the mutein is one that exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 95-156. In a yet more preferred embodiment, the mutein exhibits at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97%, 98%, 99% or 99.5% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 95-156.

A mutein may be produced by isolation from a naturally occurring mutant cell, tissue or organism. A mutein may be produced by isolation from a cell, tissue or organism that has been experimentally mutagenized. Alternatively, a mutein may be produced by chemical manipulation of a polypeptide, such as by altering the amino acid residue to another amino acid residue using synthetic or semi-synthetic chemical techniques. In a preferred embodiment, a mutein is produced from a host cell comprising a mutated nucleic acid molecule compared to the naturally occurring nucleic acid molecule. For instance, one may produce a mutein of a polypeptide by introducing one or more mutations into a nucleic acid molecule of the invention and then expressing it recombinantly. These mutations may be targeted, in which particular encoded amino acids are altered, or may be untargeted, in which random encoded amino acids within the polypeptide are altered. Muteins with random amino acid alterations can be screened for a particular biological activity or property, particularly whether the polypeptide is breast-specific, as described below. Multiple random mutations can be introduced into the gene by methods well known to the art, e.g., by error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, *in vivo* mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis and site-specific mutagenesis. Methods of producing muteins with targeted or random amino acid alterations are well known in the art. See, e.g., Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), as well as U.S. Patent No. 5,223,408, which is herein incorporated by reference in its entirety.

The invention also contemplates polypeptides that are homologous to a polypeptide of the invention. In a preferred embodiment, the polypeptide is homologous to a BSP. In an even more preferred embodiment, the polypeptide is homologous to a

BSP selected from the group having an amino acid sequence of SEQ ID NO: 95-156. By homologous polypeptide it is means one that exhibits significant sequence identity to a BSP, preferably a BSP having an amino acid sequence of SEQ ID NO: 95-156. By significant sequence identity it is meant that the homologous polypeptide exhibits at least 5% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 95-156. More preferred are homologous polypeptides exhibiting at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97% or 98% sequence identity to 10 a BSP comprising an amino acid sequence of SEQ ID NO: 95-156. Most preferably, the homologous polypeptide exhibits at least 99%, more preferably 99.5%, even more preferably 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 95-156. In a preferred embodiment, the amino acid substitutions of the homologous polypeptide are conservative amino acid substitutions as 15 discussed above.

Homologous polypeptides of the present invention also comprise polypeptide encoded by a nucleic acid molecule that selectively hybridizes to a BSNA or an antisense sequence thereof. In this embodiment, it is preferred that the homologous polypeptide be encoded by a nucleic acid molecule that hybridizes to a BSNA under low stringency, 20 moderate stringency or high stringency conditions, as defined herein. More preferred is a homologous polypeptide encoded by a nucleic acid sequence which hybridizes to a BSNA selected from the group consisting of SEQ ID NO: 1-94 or a homologous polypeptide encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule that encodes a BSP, preferably an BSP of SEQ ID NO:95-156 under low stringency, moderate 25 stringency or high stringency conditions, as defined herein.

Homologous polypeptides of the present invention may be naturally occurring and derived from another species, especially one derived from another primate, such as chimpanzee, gorilla, rhesus macaque, or baboon, wherein the homologous polypeptide comprises an amino acid sequence that exhibits significant sequence identity to that of 30 SEQ ID NO: 95-156. The homologous polypeptide may also be a naturally occurring polypeptide from a human, when the BSP is a member of a family of polypeptides. The homologous polypeptide may also be a naturally occurring polypeptide derived from a non-primate, mammalian species, including without limitation, domesticated species, e.g.,

dog, cat, mouse, rat, rabbit, guinea pig, hamster, cow, horse, goat or pig. The homologous polypeptide may also be a naturally occurring polypeptide derived from a non-mammalian species, such as birds or reptiles. The naturally occurring homologous protein may be isolated directly from humans or other species. Alternatively, the nucleic acid molecule 5 encoding the naturally occurring homologous polypeptide may be isolated and used to express the homologous polypeptide recombinantly. The homologous polypeptide may also be one that is experimentally produced by random mutation of a nucleic acid molecule and subsequent expression of the nucleic acid molecule. Alternatively, the homologous polypeptide may be one that is experimentally produced by directed mutation 10 of one or more codons to alter the encoded amino acid of a BSP. In a preferred embodiment, the homologous polypeptide encodes a polypeptide that is a BSP.

Relatedness of proteins can also be characterized using a second functional test, the ability of a first protein competitively to inhibit the binding of a second protein to an antibody. It is, therefore, another aspect of the present invention to provide isolated 15 polypeptide not only identical in sequence to those described with particularity herein, but also to provide isolated polypeptide ("cross-reactive proteins") that competitively inhibit the binding of antibodies to all or to a portion of various of the isolated polypeptides of the present invention. Such competitive inhibition can readily be determined using immunoassays well known in the art.

As discussed above, single nucleotide polymorphisms (SNPs) occur frequently in 20 eukaryotic genomes, and the sequence determined from one individual of a species may differ from other allelic forms present within the population. Thus, polypeptides of the present invention are also inclusive of those encoded by an allelic variant of a nucleic acid molecule encoding a BSP. In this embodiment, it is preferred that the polypeptide be 25 encoded by an allelic variant of a gene that encodes a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO: 95-156. More preferred is that the polypeptide be encoded by an allelic variant of a gene that has the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1-94.

Polypeptides of the present invention are also inclusive of derivative polypeptides 30 encoded by a nucleic acid molecule according to the instant invention. In this embodiment, it is preferred that the polypeptide be a BSP. Also preferred are derivative polypeptides having an amino acid sequence selected from the group consisting of SEQ ID NO: 95-156 and which has been acetylated, carboxylated, phosphorylated,

glycosylated, ubiquitinated or other PTMs. In another preferred embodiment, the derivative has been labeled with, *e.g.*, radioactive isotopes such as  $^{125}\text{I}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , and  $^3\text{H}$ . In another preferred embodiment, the derivative has been labeled with fluorophores, chemiluminescent agents, enzymes, and antiligands that can serve as specific binding pair members for a labeled ligand.

Polypeptide modifications are well known to those of skill and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as, for instance Creighton, Protein Structure and Molecular Properties, 2nd ed., W. H. Freeman and Company (1993). Many detailed reviews are available on this subject, such as, for example, those provided by Wold, in Johnson (ed.), Posttranslational Covalent Modification of Proteins, pgs. 1-12, Academic Press (1983); Seifter *et al.*, *Meth. Enzymol.* 182: 626-646 (1990) and Rattan *et al.*, *Ann. N.Y. Acad. Sci.* 663: 48-62 (1992).

One may determine whether a polypeptide of the invention is likely to be post-translationally modified by analyzing the sequence of the polypeptide to determine if there are peptide motifs indicative of sites for post-translational modification. There are a number of computer programs that permit prediction of post-translational modifications. See, *e.g.*, www.expasy.org (accessed November 11, 2002), which includes PSORT, for prediction of protein sorting signals and localization sites, SignalP, for prediction of signal peptide cleavage sites, MITOPROT and Predotar, for prediction of mitochondrial targeting sequences, NetOGlyc, for prediction of type O-glycosylation sites in mammalian proteins, big-PI Predictor and DGPI, for prediction of prenylation-anchor and cleavage sites, and NetPhos, for prediction of Ser, Thr and Tyr phosphorylation sites in eukaryotic proteins. Other computer programs, such as those included in GCG, also may be used to determine post-translational modification peptide motifs.

General examples of types of post-translational modifications include, but are not limited to: (Z)-dehydrobutyryne; 1-chondroitin sulfate-L-aspartic acid ester; 1'-glycosyl-L-tryptophan; 1'-phospho-L-histidine; 1-thioglycine; 2'-(S-L-cysteinyl)-L-histidine; 2'-[3-carboxamido (trimethylammonio)propyl]-L-histidine; 2'-alpha-mannosyl-L-tryptophan; 2-methyl-L-glutamine; 2-oxobutanoic acid; 2-pyrrolidone carboxylic acid; 3'-(1'-L-histidyl)-L-tyrosine; 3'-(8alpha-FAD)-L-histidine; 3'-(S-L-cysteinyl)-L-tyrosine; 3', 3", 5'-triiodo-L-

thyronine; 3'-4'-phospho-L-tyrosine; 3-hydroxy-L-proline; 3'-methyl-L-histidine; 3-methyl-L-lanthionine; 3'-phospho-L-histidine; 4'-(L-tryptophan)-L-tryptophyl quinone; 42 N-cysteinyl-glycosylphosphatidylinositolethanolamine; 43 -(T-L-histidyl)-L-tyrosine; 4-hydroxy-L-arginine; 4-hydroxy-L-lysine; 4-hydroxy-L-proline; 5'-(N6-L-lysine)-L-topoquinone; 5-hydroxy-L-lysine; 5-methyl-L-arginine; alpha-L-microglobulin-Ig alpha complex chromophore; bis-L-cysteinyl bis-L-histidino diiron disulfide; bis-L--cysteinyl-L-N3'-histidino-L-serinyl tetrairon' tetrasulfide; chondroitin sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-alanine; D-allo-isoleucine; D-asparagine; dehydroalanine; dehydrotyrosine; dermatan 4-sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-glucuronyl-N-glycine; dipyrrolylmethanemethyl-L-cysteine; D-leucine; D-methionine; D-phenylalanine; D-serine; D-tryptophan; glycine amide; glycine oxazolecarboxylic acid; glycine thiazolecarboxylic acid; heme P450-bis-L-cysteine-L-tyrosine; heme-bis-L-cysteine; hemediol-L-aspartyl ester-L-glutamyl ester; hemediol-L-aspartyl ester-L-glutamyl ester-L-methionine sulfonium; heme-L-cysteine; heme-L-histidine; heparan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; heme P450-bis-L-cysteine-L-lysine; hexakis-L-cysteinyl hexairon hexasulfide; keratan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-threonine; L-oxoalanine- lactic acid; L phenyllactic acid; l'-(8alpha-FAD)-L-histidine; L-2'.4',5'-topoquinone; L-3',4'-dihydroxyphenylalanine; L-3'.4'.5'-trihydroxyphenylalanine; L-4'-bromophenylalanine; L-6'-bromotryptophan; L-alanine amide; L-alanyl imidazolinone glycine; L-allysine; L-arginine amide; L-asparagine amide; L-aspartic 4-phosphoric anhydride; L-aspartic acid 1-amide; L-beta-methylthioaspartic acid; L-bromohistidine; L-citrulline; L-cysteine amide; L-cysteine glutathione disulfide; L-cysteine methyl disulfide; L-cysteine methyl ester; L-cysteine oxazolecarboxylic acid; L-cysteine oxazolinecarboxylic acid; L-cysteine persulfide; L-cysteine sulfenic acid; L-cysteine sulfinic acid; L-cysteine thiazolecarboxylic acid; L-cysteinyl homocitryl molybdenum-heptairon-nonasulfide; L-cysteinyl imidazolinone glycine; L-cysteinyl molybdopterin; L-cysteinyl molybdopterin guanine dinucleotide; L-cystine; L-erythro-beta-hydroxyasparagine; L-erythro-beta-hydroxyaspartic acid; L-gamma-carboxyglutamic acid; L-glutamic acid 1-amide; L-glutamic acid 5-methyl ester; L-glutamine amide; L-glutamyl 5-glycerylphosphorylethanolarnine; L-histidine amide; L-isoglutamyl-polyglutamic acid; L-isoglutamyl-polyglycine; L-isoleucine amide; L-lanthionine; L-leucine amide; L-lysine amide; L-lysine thiazolecarboxylic acid; L-lysinoalanine; L-methionine amide; L-

methionine sulfone; L-phenylalanine thiazolecarboxylic acid; L-phenylalanine amide; L-proline amide; L-selenocysteine; L-selenocysteinyl molybdopterin guanine dinucleotide; L-serine amide; L-serine thiazolecarboxylic acid; L-seryl imidazolinone glycine; L-T-bromophenylalanine; L-T-bromophenylalanine; L-threonine amide; L-thyroxine; L-tryptophan amide; L-tryptophyl quinone; L-tyrosine amide; L-valine amide; meso-lanthionine; N-(L-glutamyl)-L-tyrosine; N-(L-isoaspartyl)-glycine; N-(L-isoaspartyl)-L-cysteine; N,N,N-trimethyl-L-alanine; N,N-dimethyl-L-proline; N2-acetyl-L-lysine; N2-succinyl-L-tryptophan; N4-(ADP-ribosyl)-L-asparagine; N4-glycosyl-L-asparagine; N4-hydroxymethyl-L-asparagine; N4-methyl-L-asparagine; N5-methyl-L-glutamine; N6-1-carboxyethyl-L-lysine; N6-(4-amino hydroxybutyl)-L-lysine; N6-(L-isoglutamyl)-L-lysine; N6-(phospho-5'-adenosine)-L-lysine; N6-(phospho-5'-guanosine)-L-lysine; N6,N6,N6-trimethyl-L-lysine; N6,N6-dimethyl-L-lysine; N6-acetyl-L-lysine; N6-biotinyl-L-lysine; N6-carboxy-L-lysine; N6-formyl-L-lysine; N6-glycyl-L-lysine; N6-lipoyl-L-lysine; N6-methyl-L-lysine; N6-methyl-N6-poly(N-methyl-propylamine)-L-lysine; N6-mureinyl-L-lysine; N6-myristoyl-L-lysine; N6-palmitoyl-L-lysine; N6-pyridoxal phosphate-L-lysine; N6-pyruvic acid 2-iminyl-L-lysine; N6-retinal-L-lysine; N-acetylglycine; N-acetyl-L-glutamine; N-acetyl-L-alanine; N-acetyl-L-aspartic acid; N-acetyl-L-cysteine; N-acetyl-L-glutamic acid; N-acetyl-L-isoleucine; N-acetyl-L-methionine; N-acetyl-L-proline; N-acetyl-L-serine; N-acetyl-L-threonine; N-acetyl-L-tyrosine; N-acetyl-L-valine; N-alanyl-glycosylphosphatidylinositolethanolamine; N-asparaginyl-glycosylphosphatidylinositolethanolamine; N-aspartyl-glycosylphosphatidylinositolethanolamine; N-formylglycine; N-formyl-L-methionine; N-glycyl-glycosylphosphatidylinositolethanolamine; N-L-glutamyl-poly-L-glutamic acid; N-methylglycine; N-methyl-L-alanine; N-methyl-L-methionine; N-methyl-L-phenylalanine; N-myristoyl-glycine; N-palmitoyl-L-cysteine; N-pyruvic acid 2-iminyl-L-cysteine; N-pyruvic acid 2-iminyl-L-valine; N-seryl-glycosylphosphatidylinositolethanolamine; N-seryl-glycosyBSPhingolipidinositolethanolamine; O-(ADP-ribosyl)-L-serine; O-(phospho-5'-adenosine)-L-threonine; O-(phospho-5'-DNA)-L-serine; O-(phospho-5'-DNA)-L-threonine; O-(phospho-5'rRNA)-L-serine; O-(phosphoribosyl dephospho-coenzyme A)-L-serine; O-(sn-1-glycerophosphoryl)-L-serine; O4'-(8alpha-FAD)-L-tyrosine; O4'-(phospho-5'-adenosine)-L-tyrosine; O4'-(phospho-5'-DNA)-L-tyrosine; O4'-(phospho-5'-RNA)-L-tyrosine; O4'-(phospho-5'-uridine)-L-tyrosine; O4-glycosyl-L-hydroxyproline; O4'-glycosyl-L-tyrosine; O4'-sulfo-L-tyrosine; O5-glycosyl-L-hydroxylysine; O-glycosyl-L-

serine; O-glycosyl-L-threonine; omega-N-(ADP-ribosyl)-L-arginine; omega-N-omega-N'-dimethyl-L-arginine; omega-N-methyl-L-arginine; omega-N-omega-N-dimethyl-L-arginine; omega-N-phospho-L-arginine; O'octanoyl-L-serine; O-palmitoyl-L-serine; O-palmitoyl-L-threonine; O-phospho-L-serine; O-phospho-L-threonine; O-

5 phosphopantetheine-L-serine; phycoerythrobilin-bis-L-cysteine; phycourobilin-bis-L-cysteine; pyrroloquinoline quinone; pyruvic acid; S hydroxycinnamyl-L-cysteine; S-(2-aminovinyl) methyl-D-cysteine; S-(2-aminovinyl)-D-cysteine; S-(6-FW-L-cysteine; S-(8alpha-FAD)-L-cysteine; S-(ADP-ribosyl)-L-cysteine; S-(L-isoglutamyl)-L-cysteine; S-12-hydroxyfarnesyl-L-cysteine; S-acetyl-L-cysteine; S-diacylglycerol-L-cysteine; S-

10 diphytanylglycerol diether-L-cysteine; S-farnesyl-L-cysteine; S-geranylgeranyl-L-cysteine; S-glycosyl-L-cysteine; S-glycyl-L-cysteine; S-methyl-L-cysteine; S-nitrosyl-L-cysteine; S-palmitoyl-L-cysteine; S-phospho-L-cysteine; S-phycobiliviolin-L-cysteine; S-phycocyanobilin-L-cysteine; S-phycoerythrobilin-L-cysteine; S-phytochromobilin-L-cysteine; S-selenyl-L-cysteine; S-sulfo-L-cysteine; tetrakis-L-cysteinyl diiron disulfide;

15 tetrakis-L-cysteinyl iron; tetrakis-L-cysteinyl tetrairon tetrasulfide; trans-2,3-cis 4-dihydroxy-L-proline; tris-L-cysteinyl triiron tetrasulfide; tris-L-cysteinyl triiron trisulfide; tris-L-cysteinyl-L-aspartato tetrairon tetrasulfide; tris-L-cysteinyl-L-cysteine persulfido-bis-L-glutamato-L-histidino tetrairon disulfide trioxide; tris-L-cysteinyl-L-N3'-histidino tetrairon tetrasulfide; tris-L-cysteinyl-L-N1'-histidino tetrairon tetrasulfide; and tris-L-

20 cysteinyl-L-serinyl tetrairon tetrasulfide.

Additional examples of PTMs may be found in web sites such as the Delta Mass database based on Krishna, R. G. and F. Wold (1998). Posttranslational Modifications. Proteins - Analysis and Design. R. H. Angeletti. San Diego, Academic Press. 1: 121-206. ; Methods in Enzymology, 193, J.A. McClosky (ed) (1990), pages 647-660; Methods in Protein Sequence Analysis edited by Kazutomo Imahori and Fumio Sakiyama, Plenum Press, (1993) "Post-translational modifications of proteins" R.G. Krishna and F. Wold pages 167-172; "GlycoSuiteDB: a new curated relational database of glycoprotein glycan structures and their biological sources" Cooper et al. Nucleic Acids Res. 29; 332-335 (2001) "O-GLYCBASE version 4.0: a revised database of O-glycosylated proteins" Gupta et al. Nucleic Acids Research, 27: 370-372 (1999); and "PhosphoBase, a database of phosphorylation sites: release 2.0.", Kreegipuu et al. Nucleic Acids Res 27(1):237-239 (1999) see also, WO 02/21139A2, the disclosure of which is incorporated herein by reference in its entirety.

Tumorigenesis is often accompanied by alterations in the post-translational modifications of proteins. Thus, in another embodiment, the invention provides polypeptides from cancerous cells or tissues that have altered post-translational modifications compared to the post-translational modifications of polypeptides from normal cells or tissues. A number of altered post-translational modifications are known. One common alteration is a change in phosphorylation state, wherein the polypeptide from the cancerous cell or tissue is hyperphosphorylated or hypophosphorylated compared to the polypeptide from a normal tissue, or wherein the polypeptide is phosphorylated on different residues than the polypeptide from a normal cell. Another common alteration is a change in glycosylation state, wherein the polypeptide from the cancerous cell or tissue has more or less glycosylation than the polypeptide from a normal tissue, and/or wherein the polypeptide from the cancerous cell or tissue has a different type of glycosylation than the polypeptide from a noncancerous cell or tissue. Changes in glycosylation may be critical because carbohydrate-protein and carbohydrate-carbohydrate interactions are important in cancer cell progression, dissemination and invasion. See, e.g., Barchi, *Curr. Pharm. Des.* 6: 485-501 (2000), Verma, *Cancer Biochem. Biophys.* 14: 151-162 (1994) and Dennis et al., *Bioessays* 5: 412-421 (1999).

Another post-translational modification that may be altered in cancer cells is prenylation. Prenylation is the covalent attachment of a hydrophobic prenyl group (either farnesyl or geranylgeranyl) to a polypeptide. Prenylation is required for localizing a protein to a cell membrane and is often required for polypeptide function. For instance, the Ras superfamily of GTPase signalling proteins must be prenylated for function in a cell. See, e.g., Prendergast et al., *Semin. Cancer Biol.* 10: 443-452 (2000) and Khwaja et al., *Lancet* 355: 741-744 (2000).

Other post-translation modifications that may be altered in cancer cells include, without limitation, polypeptide methylation, acetylation, arginylation or racemization of amino acid residues. In these cases, the polypeptide from the cancerous cell may exhibit either increased or decreased amounts of the post-translational modification compared to the corresponding polypeptides from noncancerous cells.

Other polypeptide alterations in cancer cells include abnormal polypeptide cleavage of proteins and aberrant protein-protein interactions. Abnormal polypeptide cleavage may be cleavage of a polypeptide in a cancerous cell that does not usually occur in a normal cell, or a lack of cleavage in a cancerous cell, wherein the polypeptide is

cleaved in a normal cell. Aberrant protein-protein interactions may be either covalent cross-linking or non-covalent binding between proteins that do not normally bind to each other. Alternatively, in a cancerous cell, a protein may fail to bind to another protein to which it is bound in a noncancerous cell. Alterations in cleavage or in protein-protein interactions may be due to over- or underproduction of a polypeptide in a cancerous cell compared to that in a normal cell, or may be due to alterations in post-translational modifications (see above) of one or more proteins in the cancerous cell. See, e.g., Henschchen-Edman, *Ann. N.Y. Acad. Sci.* 936: 580-593 (2001).

Alterations in polypeptide post-translational modifications, as well as changes in polypeptide cleavage and protein-protein interactions, may be determined by any method known in the art. For instance, alterations in phosphorylation may be determined by using anti-phosphoserine, anti-phosphothreonine or anti-phosphotyrosine antibodies or by amino acid analysis. Glycosylation alterations may be determined using antibodies specific for different sugar residues, by carbohydrate sequencing, or by alterations in the size of the glycoprotein, which can be determined by, e.g., SDS polyacrylamide gel electrophoresis (PAGE). Other alterations of post-translational modifications, such as prenylation, racemization, methylation, acetylation and arginylation, may be determined by chemical analysis, protein sequencing, amino acid analysis, or by using antibodies specific for the particular post-translational modifications. Changes in protein-protein interactions and in polypeptide cleavage may be analyzed by any method known in the art including, without limitation, non-denaturing PAGE (for non-covalent protein-protein interactions), SDS PAGE (for covalent protein-protein interactions and protein cleavage), chemical cleavage, protein sequencing or immunoassays.

In another embodiment, the invention provides polypeptides that have been post-translationally modified. In one embodiment, polypeptides may be modified enzymatically or chemically, by addition or removal of a post-translational modification. For example, a polypeptide may be glycosylated or deglycosylated enzymatically. Similarly, polypeptides may be phosphorylated using a purified kinase, such as a MAP kinase (e.g, p38, ERK, or JNK) or a tyrosine kinase (e.g., Src or erbB2). A polypeptide may also be modified through synthetic chemistry. Alternatively, one may isolate the polypeptide of interest from a cell or tissue that expresses the polypeptide with the desired post-translational modification. In another embodiment, a nucleic acid molecule encoding the polypeptide of interest is introduced into a host cell that is capable of post-

translationally modifying the encoded polypeptide in the desired fashion. If the polypeptide does not contain a motif for a desired post-translational modification, one may alter the post-translational modification by mutating the nucleic acid sequence of a nucleic acid molecule encoding the polypeptide so that it contains a site for the desired post- 5 translational modification. Amino acid sequences that may be post-translationally modified are known in the art. See, e.g., the programs described above on the website [www.expasy.org](http://www.expasy.org). The nucleic acid molecule may also be introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide. Similarly, one may delete sites that are post-translationally modified by either mutating the nucleic acid 10 sequence so that the encoded polypeptide does not contain the post-translational modification motif, or by introducing the native nucleic acid molecule into a host cell that is not capable of post-translationally modifying the encoded polypeptide.

It will be appreciated, as is well known and as noted above, that polypeptides are not always entirely linear. For instance, polypeptides may be branched as a result of 15 ubiquitination, and they may be circular, with or without branching, generally as a result of posttranslational events, including natural processing event and events brought about by human manipulation which do not occur naturally. Circular, branched and branched circular polypeptides may be synthesized by non-translation natural process and by entirely synthetic methods, as well. Modifications can occur anywhere in a polypeptide, 20 including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. In fact, blockage of the amino or carboxyl group in a polypeptide, or both, by a covalent modification, is common in naturally occurring and synthetic polypeptides and such modifications may be present in polypeptides of the present invention, as well. For instance, the amino terminal residue of polypeptides made in *E. coli*, prior to proteolytic 25 processing, almost invariably will be N-formylmethionine.

Useful post-synthetic (and post-translational) modifications include conjugation to detectable labels, such as fluorophores. A wide variety of amine-reactive and thiol-reactive fluorophore derivatives have been synthesized that react under nondenaturing conditions with N-terminal amino groups and epsilon amino groups of lysine residues, on 30 the one hand, and with free thiol groups of cysteine residues, on the other.

Kits are available commercially that permit conjugation of proteins to a variety of amine-reactive or thiol-reactive fluorophores: Molecular Probes, Inc. (Eugene, OR, USA), e.g., offers kits for conjugating proteins to Alexa Fluor 350, Alexa Fluor 430,

Fluorescein-EX, Alexa Fluor 488, Oregon Green 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, and Texas Red-X.

- A wide variety of other amine-reactive and thiol-reactive fluorophores are available commercially (Molecular Probes, Inc., Eugene, OR, USA), including Alexa 5 Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 10 TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA).

The polypeptides of the present invention can also be conjugated to fluorophores, 15 other proteins, and other macromolecules, using bifunctional linking reagents. Common homobifunctional reagents include, *e.g.*, APG, AEDP, BASED, BMB, BMDB, BMH, BMOE, BM[PEO]3, BM[PEO]4, BS3, BSOCOES, DFDNB, DMA, DMP, DMS, DPDPB, DSG, DSP (Lomant's Reagent), DSS, DST, DTBP, DTME, DTSSP, EGS, HBVS, Sulfo-BSOCOES, Sulfo-DST, Sulfo-EGS (all available from Pierce, Rockford, IL, USA); 20 common heterobifunctional cross-linkers include ABH, AMAS, ANB-NOS, APDP, ASBA, BMPA, BMPH, BMPS, EDC, EMCA, EMCH, EMCS, KMUA, KMUH, GMBS, LC-SMCC, LC-SPDP, MBS, M2C2H, MPBH, MSA, NHS-ASA, PDPH, PMPI, SADP, SAED, SAND, SANPAH, SASD, SATP, SBAP, SFAD, SIA, SIAB, SMCC, SMPB, SMPH, SMPT, SPDP, Sulfo-EMCS, Sulfo-GMBS, Sulfo-HSAB, Sulfo-KMUS, 25 Sulfo-LC-SPDP, Sulfo-MBS, Sulfo-NHS-LC-ASA, Sulfo-SADP, Sulfo-SANPAH, Sulfo-SIAB, Sulfo-SMCC, Sulfo-SMPB, Sulfo-LC-SMPT, SVSB, TFCS (all available Pierce, Rockford, IL, USA).

Polypeptides of the present invention, including full length polypeptides, 30 fragments and fusion proteins, can be conjugated, using such cross-linking reagents, to fluorophores that are not amine- or thiol-reactive. Other labels that usefully can be conjugated to polypeptides of the present invention include radioactive labels, echosonographic contrast reagents, and MRI contrast agents.

Polypeptides of the present invention, including full length polypeptide, fragments and fusion proteins, can also usefully be conjugated using cross-linking agents to carrier proteins, such as KLH, bovine thyroglobulin, and even bovine serum albumin (BSA), to increase immunogenicity for raising anti-BSP antibodies.

5 Polypeptides of the present invention, including full length polypeptide, fragments and fusion proteins, can also usefully be conjugated to polyethylene glycol (PEG); PEGylation increases the serum half life of proteins administered intravenously for replacement therapy. Delgado *et al.*, *Crit. Rev. Ther. Drug Carrier Syst.* 9(3-4): 249-304 (1992); Scott *et al.*, *Curr. Pharm. Des.* 4(6): 423-38 (1998); De Santis *et al.*, *Curr. Opin. Biotechnol.* 10(4): 324-30 (1999). PEG monomers can be attached to the protein directly or through a linker, with PEGylation using PEG monomers activated with tresyl chloride (2,2,2-trifluoroethanesulphonyl chloride) permitting direct attachment under mild conditions.

10 Polypeptides of the present invention are also inclusive of analogs of a polypeptide encoded by a nucleic acid molecule according to the instant invention. In a preferred embodiment, this polypeptide is a BSP. In a more preferred embodiment, this polypeptide is derived from a polypeptide having part or all of the amino acid sequence of SEQ ID NO: 95-156. Also preferred is an analog polypeptide comprising one or more substitutions of non-natural amino acids or non-native inter-residue bonds compared to the naturally occurring polypeptide. In one embodiment, the analog is structurally similar to a BSP, but one or more peptide linkages is replaced by a linkage selected from the group consisting of --CH<sub>2</sub>NH--, --CH<sub>2</sub>S--, --CH<sub>2</sub>-CH<sub>2</sub>--, --CH=CH--(cis and trans), --COCH<sub>2</sub>--, --CH(OH)CH<sub>2</sub>-- and --CH<sub>2</sub>SO--. In another embodiment, the analog comprises substitution of one or more amino acids of a BSP with a D-amino acid of the same type or other non-natural amino acid in order to generate more stable peptides. D-amino acids can readily be incorporated during chemical peptide synthesis: peptides assembled from D-amino acids are more resistant to proteolytic attack; incorporation of D-amino acids can also be used to confer specific three-dimensional conformations on the peptide. Other amino acid analogues commonly added during chemical synthesis include ornithine, norleucine, phosphorylated amino acids (typically phosphoserine, phosphothreonine, phosphotyrosine), L-malonyltyrosine, a non-hydrolyzable analog of phosphotyrosine (*see*,

e.g., Kole *et al.*, *Biochem. Biophys. Res. Com.* 209: 817-821 (1995)), and various halogenated phenylalanine derivatives.

Non-natural amino acids can be incorporated during solid phase chemical synthesis or by recombinant techniques, although the former is typically more common. Solid phase chemical synthesis of peptides is well established in the art. Procedures are described, *inter alia*, in Chan *et al.* (eds.), Fmoc Solid Phase Peptide Synthesis: A Practical Approach (Practical Approach Series), Oxford Univ. Press (March 2000); Jones, Amino Acid and Peptide Synthesis (Oxford Chemistry Primers, No 7), Oxford Univ. Press (1992); and Bodanszky, Principles of Peptide Synthesis (Springer Laboratory), Springer Verlag (1993).

Amino acid analogues having detectable labels are also usefully incorporated during synthesis to provide derivatives and analogs. Biotin, for example can be added using biotinoyl--(9-fluorenylmethoxycarbonyl)-L-lysine (FMOC biocytin) (Molecular Probes, Eugene, OR, USA). Biotin can also be added enzymatically by incorporation into a fusion protein of a *E. coli* BirA substrate peptide. The FMOC and *t*BOC derivatives of dabcyll-L-lysine (Molecular Probes, Inc., Eugene, OR, USA) can be used to incorporate the dabcyll chromophore at selected sites in the peptide sequence during synthesis. The aminonaphthalene derivative EDANS, the most common fluorophore for pairing with the dabcyll quencher in fluorescence resonance energy transfer (FRET) systems, can be introduced during automated synthesis of peptides by using EDANS--FMOC-L-glutamic acid or the corresponding *t*BOC derivative (both from Molecular Probes, Inc., Eugene, OR, USA). Tetramethylrhodamine fluorophores can be incorporated during automated FMOC synthesis of peptides using (FMOC)--TMR-L-lysine (Molecular Probes, Inc. Eugene, OR, USA).

Other useful amino acid analogues that can be incorporated during chemical synthesis include aspartic acid, glutamic acid, lysine, and tyrosine analogues having allyl side-chain protection (Applied Biosystems, Inc., Foster City, CA, USA); the allyl side chain permits synthesis of cyclic, branched-chain, sulfonated, glycosylated, and phosphorylated peptides.

A large number of other FMOC-protected non-natural amino acid analogues capable of incorporation during chemical synthesis are available commercially, including, e.g., Fmoc-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid, Fmoc-3-endo-aminobicyclo[2.2.1]heptane-2-endo-carboxylic acid, Fmoc-3-exo-

aminobicyclo[2.2.1]heptane-2-exo-carboxylic acid, Fmoc-3-endo-amino-  
bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid, Fmoc-3-exo-amino-bicyclo[2.2.1]hept-  
5-ene-2-exo-carboxylic acid, Fmoc-cis-2-amino-1-cyclohexanecarboxylic acid, Fmoc-  
trans-2-amino-1-cyclohexanecarboxylic acid, Fmoc-1-amino-1-cyclopentanecarboxylic  
5 acid, Fmoc-cis-2-amino-1-cyclopentanecarboxylic acid, Fmoc-1-amino-1-  
cyclopropanecarboxylic acid, Fmoc-D-2-amino-4-(ethylthio)butyric acid, Fmoc-L-2-  
amino-4-(ethylthio)butyric acid, Fmoc-L-buthionine, Fmoc-S-methyl-L-Cysteine, Fmoc-  
2-aminobenzoic acid (anthranillic acid), Fmoc-3-aminobenzoic acid, Fmoc-4-  
aminobenzoic acid, Fmoc-2-aminobenzophenone-2'-carboxylic acid, Fmoc-N-(4-  
10 aminobenzoyl)-β-alanine, Fmoc-2-amino-4,5-dimethoxybenzoic acid, Fmoc-4-  
aminohippuric acid, Fmoc-2-amino-3-hydroxybenzoic acid, Fmoc-2-amino-5-  
hydroxybenzoic acid, Fmoc-3-amino-4-hydroxybenzoic acid, Fmoc-4-amino-3-  
hydroxybenzoic acid, Fmoc-4-amino-2-hydroxybenzoic acid, Fmoc-5-amino-2-  
hydroxybenzoic acid, Fmoc-2-amino-3-methoxybenzoic acid, Fmoc-4-amino-3-  
15 methoxybenzoic acid, Fmoc-2-amino-3-methylbenzoic acid, Fmoc-2-amino-5-  
methylbenzoic acid, Fmoc-2-amino-6-methylbenzoic acid, Fmoc-3-amino-2-  
methylbenzoic acid, Fmoc-3-amino-4-methylbenzoic acid, Fmoc-4-amino-3-  
methylbenzoic acid, Fmoc-3-amino-2-naphtoic acid, Fmoc-D,L-3-amino-3-  
phenylpropionic acid, Fmoc-L-Methyldopa, Fmoc-2-amino-4,6-dimethyl-3-  
20 pyridinecarboxylic acid, Fmoc-D,L-amino-2-thiophenacetic acid, Fmoc-4-  
(carboxymethyl)piperazine, Fmoc-4-carboxypiperazine, Fmoc-4-  
(carboxymethyl)homopiperazine, Fmoc-4-phenyl-4-piperidinecarboxylic acid, Fmoc-L-  
1,2,3,4-tetrahydronorharman-3-carboxylic acid, Fmoc-L-thiazolidine-4-carboxylic acid, all  
available from The Peptide Laboratory (Richmond, CA, USA).

25 Non-natural residues can also be added biosynthetically by engineering a  
suppressor tRNA, typically one that recognizes the UAG stop codon, by chemical  
aminoacylation with the desired unnatural amino acid. Conventional site-directed  
mutagenesis is used to introduce the chosen stop codon UAG at the site of interest in the  
protein gene. When the acylated suppressor tRNA and the mutant gene are combined in  
30 an *in vitro* transcription/translation system, the unnatural amino acid is incorporated in  
response to the UAG codon to give a protein containing that amino acid at the specified  
position. Liu *et al.*, *Proc. Natl Acad. Sci. USA* 96(9): 4780-5 (1999); Wang *et al.*, *Science*  
292(5516): 498-500 (2001).

*Fusion Proteins*

Another aspect of the present invention relates to the fusion of a polypeptide of the present invention to heterologous polypeptides. In a preferred embodiment, the polypeptide of the present invention is a BSP. In a more preferred embodiment, the 5 polypeptide of the present invention that is fused to a heterologous polypeptide comprises part or all of the amino acid sequence of SEQ ID NO: 95-156, or is a mutein, homologous polypeptide, analog or derivative thereof. In an even more preferred embodiment, the fusion protein is encoded by a nucleic acid molecule comprising all or part of the nucleic acid sequence of SEQ ID NO: 1-94, or comprises all or part of a nucleic acid sequence 10 that selectively hybridizes or is homologous to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94.

The fusion proteins of the present invention will include at least one fragment of a polypeptide of the present invention, which fragment is at least 6, typically at least 8, often at least 15, and usefully at least 16, 17, 18, 19, or 20 amino acids long. The fragment of 15 the polypeptide of the present to be included in the fusion can usefully be at least 25 amino acids long, at least 50 amino acids long, and can be at least 75, 100, or even 150 amino acids long. Fusions that include the entirety of a polypeptide of the present invention have particular utility.

The heterologous polypeptide included within the fusion protein of the present 20 invention is at least 6 amino acids in length, often at least 8 amino acids in length, and preferably at least 15, 20, or 25 amino acids in length. Fusions that include larger polypeptides, such as the IgG Fc region, and even entire proteins (such as GFP chromophore-containing proteins) are particularly useful.

As described above in the description of vectors and expression vectors of the 25 present invention, which discussion is incorporated here by reference in its entirety, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those designed to facilitate purification and/or visualization of recombinantly-expressed proteins. *See, e.g., Ausubel, Chapter 16, (1992), supra.* Although purification tags can also be incorporated into fusions that are chemically 30 synthesized, chemical synthesis typically provides sufficient purity that further purification by HPLC suffices; however, visualization tags as above described retain their utility even when the protein is produced by chemical synthesis, and when so included

render the fusion proteins of the present invention useful as directly detectable markers of the presence of a polypeptide of the invention.

As also discussed above, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those that facilitate secretion of recombinantly expressed proteins into the periplasmic space or extracellular milieu for prokaryotic hosts or into the culture medium for eukaryotic cells through incorporation of secretion signals and/or leader sequences. For example, a His<sup>6</sup> tagged protein can be purified on a Ni affinity column and a GST fusion protein can be purified on a glutathione affinity column. Similarly, a fusion protein comprising the Fc domain of IgG can be purified on a Protein A or Protein G column and a fusion protein comprising an epitope tag such as myc can be purified using an immunoaffinity column containing an anti-c-myc antibody. It is preferable that the epitope tag be separated from the protein encoded by the essential gene by an enzymatic cleavage site that can be cleaved after purification. See also the discussion of nucleic acid molecules encoding fusion proteins that may be expressed on the surface of a cell.

Other useful fusion proteins of the present invention include those that permit use of the polypeptide of the present invention as bait in a yeast two-hybrid system. See Bartel *et al.* (eds.), The Yeast Two-Hybrid System, Oxford University Press (1997); Zhu *et al.*, Yeast Hybrid Technologies, Eaton Publishing (2000); Fields *et al.*, *Trends Genet.* 10(8): 286-92 (1994); Mendelsohn *et al.*, *Curr. Opin. Biotechnol.* 5(5): 482-6 (1994); Luban *et al.*, *Curr. Opin. Biotechnol.* 6(1): 59-64 (1995); Allen *et al.*, *Trends Biochem. Sci.* 20(12): 511-6 (1995); Drees, *Curr. Opin. Chem. Biol.* 3(1): 64-70 (1999); Topcu *et al.*, *Pharm. Res.* 17(9): 1049-55 (2000); Fashena *et al.*, *Gene* 250(1-2): 1-14 (2000); Colas *et al.*, *Nature* 380, 548-550 (1996); Norman, T. *et al.*, *Science* 285, 591-595 (1999); Fabbrizio *et al.*, *Oncogene* 18, 4357-4363 (1999); Xu *et al.*, *Proc Natl Acad Sci U S A.* 94, 12473-12478 (1997); Yang, *et al.*, *Nuc. Acids Res.* 23, 1152-1156 (1995); Kolonin *et al.*, *Proc Natl Acad Sci U S A* 95, 14266-14271 (1998); Cohen *et al.*, *Proc Natl Acad Sci U S A* 95, 14272-14277 (1998); Uetz, *et al.* *Nature* 403, 623-627(2000); Ito, *et al.*, *Proc Natl Acad Sci U S A* 98, 4569-4574 (2001). Typically, such fusion is to either *E. coli* LexA or yeast GAL4 DNA binding domains. Related bait plasmids are available that express the bait fused to a nuclear localization signal.

Other useful fusion proteins include those that permit display of the encoded polypeptide on the surface of a phage or cell, fusions to intrinsically fluorescent proteins,

such as green fluorescent protein (GFP), and fusions to the IgG Fc region, as described above.

The polypeptides of the present invention can also usefully be fused to protein toxins, such as *Pseudomonas* exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin 5 lethal factor, ricin, in order to effect ablation of cells that bind or take up the proteins of the present invention.

Fusion partners include, *inter alia*, *myc*, hemagglutinin (HA), GST, immunoglobulins,  $\beta$ -galactosidase, biotin trpE, protein A,  $\beta$ -lactamase,  $\alpha$ -amylase, maltose binding protein, alcohol dehydrogenase, polyhistidine (for example, six histidine 10 at the amino and/or carboxyl terminus of the polypeptide), lacZ, green fluorescent protein (GFP), yeast  $\alpha$  mating factor, GAL4 transcription activation or DNA binding domain, luciferase, and serum proteins such as ovalbumin, albumin and the constant domain of IgG. See, e.g., Ausubel (1992), *supra* and Ausubel (1999), *supra*. Fusion proteins may 15 also contain sites for specific enzymatic cleavage, such as a site that is recognized by enzymes such as Factor XIII, trypsin, pepsin, or any other enzyme known in the art. Fusion proteins will typically be made by either recombinant nucleic acid methods, as described above, chemically synthesized using techniques well known in the art (e.g., a Merrifield synthesis), or produced by chemical cross-linking.

Another advantage of fusion proteins is that the epitope tag can be used to bind the 20 fusion protein to a plate or column through an affinity linkage for screening binding proteins or other molecules that bind to the BSP.

As further described below, the polypeptides of the present invention can readily 25 be used as specific immunogens to raise antibodies that specifically recognize polypeptides of the present invention including BSPs and their allelic variants and homologues. The antibodies, in turn, can be used, *inter alia*, specifically to assay for the polypeptides of the present invention, particularly BSPs, e.g. by ELISA for detection of protein fluid samples, such as serum, by immunohistochemistry or laser scanning cytometry, for detection of protein in tissue samples, or by flow cytometry, for detection of intracellular protein in cell suspensions, for specific antibody-mediated isolation and/or 30 purification of BSPs, as for example by immunoprecipitation, and for use as specific agonists or antagonists of BSPs.

One may determine whether polypeptides of the present invention including BSPs, mutoins, homologous proteins or allelic variants or fusion proteins of the present invention

are functional by methods known in the art. For instance, residues that are tolerant of change while retaining function can be identified by altering the polypeptide at known residues using methods known in the art, such as alanine scanning mutagenesis, Cunningham *et al.*, *Science* 244(4908): 1081-5 (1989); transposon linker scanning mutagenesis, Chen *et al.*, *Gene* 263(1-2): 39-48 (2001); combinations of homolog- and alanine-scanning mutagenesis, Jin *et al.*, *J. Mol. Biol.* 226(3): 851-65 (1992); combinatorial alanine scanning, Weiss *et al.*, *Proc. Natl. Acad. Sci USA* 97(16): 8950-4 (2000), followed by functional assay. Transposon linker scanning kits are available commercially (New England Biolabs, Beverly, MA, USA, catalog. no. E7-102S; 5 EZ::TN™ In-Frame Linker Insertion Kit, catalogue no. EZI04KN, (Epicentre Technologies Corporation, Madison, WI, USA).

Purification of the polypeptides or fusion proteins of the present invention is well known and within the skill of one having ordinary skill in the art. *See, e.g.,* Scopes, Protein Purification, 2d ed. (1987). Purification of recombinantly expressed polypeptides 15 is described above. Purification of chemically-synthesized peptides can readily be effected, *e.g.*, by HPLC.

Accordingly, it is an aspect of the present invention to provide the isolated polypeptides or fusion proteins of the present invention in pure or substantially pure form in the presence of absence of a stabilizing agent. Stabilizing agents include both 20 proteinaceous and non-proteinaceous material and are well known in the art. Stabilizing agents, such as albumin and polyethylene glycol (PEG) are known and are commercially available.

Although high levels of purity are preferred when the isolated polypeptide or fusion protein of the present invention are used as therapeutic agents, such as in vaccines 25 and replacement therapy, the isolated polypeptides of the present invention are also useful at lower purity. For example, partially purified polypeptides of the present invention can be used as immunogens to raise antibodies in laboratory animals.

In a preferred embodiment, the purified and substantially purified polypeptides of the present invention are in compositions that lack detectable ampholytes, acrylamide 30 monomers, bis-acrylamide monomers, and polyacrylamide.

The polypeptides or fusion proteins of the present invention can usefully be attached to a substrate. The substrate can be porous or solid, planar or non-planar; the bond can be covalent or noncovalent. For example, the peptides of the invention may be

stabilized by covalent linkage to albumin. See, U.S. Patent No. 5,876,969, the contents of which are hereby incorporated in its entirety.

For example, the polypeptides or fusion proteins of the present invention can usefully be bound to a porous substrate, commonly a membrane, typically comprising 5 nitrocellulose, polyvinylidene fluoride (PVDF), or cationically derivatized, hydrophilic PVDF; so bound, the polypeptides or fusion proteins of the present invention can be used to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized polypeptide or fusion protein of the present invention.

As another example, the polypeptides or fusion proteins of the present invention 10 can usefully be bound to a substantially nonporous substrate, such as plastic, to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized protein of the present invention. Such plastics include polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, 15 polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof; when the assay is performed in a standard microtiter dish, the plastic is typically polystyrene.

The polypeptides and fusion proteins of the present invention can also be attached 20 to a substrate suitable for use as a surface enhanced laser desorption ionization source; so attached, the polypeptide or fusion protein of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biologic interaction there between. The polypeptides or fusion proteins of the present invention can also be attached to a 25 substrate suitable for use in surface plasmon resonance detection; so attached, the polypeptide or fusion protein of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biological interaction there between.

#### Alternative Transcripts

In another aspect, the present invention provides splice variants of genes and 30 proteins encoded thereby. The identification of a novel splice variant which encodes an amino acid sequence with a novel region can be targeted for the generation of reagents for use in detection and/or treatment of cancer. The novel amino acid sequence may lead to a unique protein structure, protein subcellular localization, biochemical processing or

function of the splice variant. This information can be used to directly or indirectly facilitate the generation of additional or novel therapeutics or diagnostics. The nucleotide sequence in this novel splice variant can be used as a nucleic acid probe for the diagnosis and/or treatment of cancer.

5 Specifically, the newly identified sequences may enable the production of new antibodies or compounds directed against the novel region for use as a therapeutic or diagnostic. Alternatively, the newly identified sequences may alter the biochemical or biological properties of the encoded protein in such a way as to enable the generation of improved or different therapeutics targeting this protein.

10 Antibodies

In another aspect, the invention provides antibodies, including fragments and derivatives thereof, that bind specifically to polypeptides encoded by the nucleic acid molecules of the invention. In a preferred embodiment, the antibodies are specific for a polypeptide that is a BSP, or a fragment, mutein, derivative, analog or fusion protein thereof. In a more preferred embodiment, the antibodies are specific for a polypeptide that comprises SEQ ID NO: 95-156, or a fragment, mutein, derivative, analog or fusion protein thereof.

The antibodies of the present invention can be specific for linear epitopes, discontinuous epitopes, or conformational epitopes of such proteins or protein fragments, either as present on the protein in its native conformation or, in some cases, as present on the proteins as denatured, as, e.g., by solubilization in SDS. New epitopes may be also due to a difference in post translational modifications (PTMs) in disease versus normal tissue. For example, a particular site on a BSP may be glycosylated in cancerous cells, but not glycosylated in normal cells or vice versa. In addition, alternative splice forms of a 25 BSP may be indicative of cancer. Differential degradation of the C or N-terminus of a BSP may also be a marker or target for anticancer therapy. For example, an BSP may be N-terminal degraded in cancer cells exposing new epitopes to which antibodies may selectively bind for diagnostic or therapeutic uses.

As is well known in the art, the degree to which an antibody can discriminate as 30 among molecular species in a mixture will depend, in part, upon the conformational relatedness of the species in the mixture; typically, the antibodies of the present invention will discriminate over adventitious binding to non-BSP polypeptides by at least two-fold,

more typically by at least 5-fold, typically by more than 10-fold, 25-fold, 50-fold, 75-fold, and often by more than 100-fold, and on occasion by more than 500-fold or 1000-fold. When used to detect the proteins or protein fragments of the present invention, the antibody of the present invention is sufficiently specific when it can be used to determine 5 the presence of the polypeptide of the present invention in samples derived from human breast.

Typically, the affinity or avidity of an antibody (or antibody multimer, as in the case of an IgM pentamer) of the present invention for a protein or protein fragment of the present invention will be at least about  $1 \times 10^{-6}$  molar (M), typically at least about  $5 \times 10^{-7}$  10 M,  $1 \times 10^{-7}$  M, with affinities and avidities of at least  $1 \times 10^{-8}$  M,  $5 \times 10^{-9}$  M,  $1 \times 10^{-10}$  M and up to  $1 \times 10^{-13}$  M proving especially useful.

The antibodies of the present invention can be naturally occurring forms, such as IgG, IgM, IgD, IgE, IgY, and IgA, from any avian, reptilian, or mammalian species.

Human antibodies can, but will infrequently, be drawn directly from human donors 15 or human cells. In such case, antibodies to the polypeptides of the present invention will typically have resulted from fortuitous immunization, such as autoimmune immunization, with the polypeptide of the present invention. Such antibodies will typically, but will not invariably, be polyclonal. In addition, individual polyclonal antibodies may be isolated and cloned to generate monoclonals.

20 Human antibodies are more frequently obtained using transgenic animals that express human immunoglobulin genes, which transgenic animals can be affirmatively immunized with the protein immunogen of the present invention. Human Ig-transgenic mice capable of producing human antibodies and methods of producing human antibodies therefrom upon specific immunization are described, *inter alia*, in U.S. Patent Nos. 25 6,162,963; 6,150,584; 6,114,598; 6,075,181; 5,939,598; 5,877,397; 5,874,299; 5,814,318; 5,789,650; 5,770,429; 5,661,016; 5,633,425; 5,625,126; 5,569,825; 5,545,807; 5,545,806, and 5,591,669, the disclosures of which are incorporated herein by reference in their entireties. Such antibodies are typically monoclonal, and are typically produced using techniques developed for production of murine antibodies.

30 Human antibodies are particularly useful, and often preferred, when the antibodies of the present invention are to be administered to human beings as *in vivo* diagnostic or therapeutic agents, since recipient immune response to the administered antibody will

often be substantially less than that occasioned by administration of an antibody derived from another species, such as mouse.

IgG, IgM, IgD, IgE, IgY, and IgA antibodies of the present invention are also usefully obtained from other species, including mammals such as rodents (typically mouse, but also rat, guinea pig, and hamster), lagomorphs (typically rabbits), and also larger mammals, such as sheep, goats, cows, and horses; or egg laying birds or reptiles such as chickens or alligators. In such cases, as with the transgenic human-antibody-producing non-human mammals, fortuitous immunization is not required, and the non-human mammal is typically affirmatively immunized, according to standard immunization protocols, with the polypeptide of the present invention. One form of avian antibodies may be generated using techniques described in WO 00/29444, published 25 May 2000.

As discussed above, virtually all fragments of 8 or more contiguous amino acids of a polypeptide of the present invention can be used effectively as immunogens when conjugated to a carrier, typically a protein such as bovine thyroglobulin, keyhole limpet hemocyanin, or bovine serum albumin, conveniently using a bifunctional linker such as those described elsewhere above, which discussion is incorporated by reference here.

Immunogenicity can also be conferred by fusion of the polypeptide of the present invention to other moieties. For example, polypeptides of the present invention can be produced by solid phase synthesis on a branched polylysine core matrix; these multiple antigenic peptides (MAPs) provide high purity, increased avidity, accurate chemical definition and improved safety in vaccine development. Tam *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5409-5413 (1988); Posnett *et al.*, *J. Biol. Chem.* 263: 1719-1725 (1988).

Protocols for immunizing non-human mammals or avian species are well-established in the art. See Harlow *et al.* (eds.), Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory (1998); Coligan *et al.* (eds.), Current Protocols in Immunology, John Wiley & Sons, Inc. (2001); Zola, Monoclonal Antibodies: Preparation and Use of Monoclonal Antibodies and Engineered Antibody Derivatives (Basics: From Background to Bench), Springer Verlag (2000); Gross M, Speck *J.Dtsch. Tierarztl. Wochenschr.* 103: 417-422 (1996). Immunization protocols often include multiple immunizations, either with or without adjuvants such as Freund's complete adjuvant and Freund's incomplete adjuvant, and may include naked DNA immunization (Moss, *Semin. Immunol.* 2: 317-327 (1990)).

Antibodies from non-human mammals and avian species can be polyclonal or monoclonal, with polyclonal antibodies having certain advantages in immunohistochemical detection of the polypeptides of the present invention and monoclonal antibodies having advantages in identifying and distinguishing particular epitopes of the polypeptides of the present invention. Antibodies from avian species may have particular advantage in detection of the polypeptides of the present invention, in human serum or tissues (Vikinge et al., *Biosens. Bioelectron.* 13: 1257-1262 (1998). Following immunization, the antibodies of the present invention can be obtained using any art-accepted technique. Such techniques are well known in the art and are described in detail in references such as Coligan, *supra*; Zola, *supra*; Howard *et al.* (eds.), Basic Methods in Antibody Production and Characterization, CRC Press (2000); Harlow, *supra*; Davis (ed.), Monoclonal Antibody Protocols, Vol. 45, Humana Press (1995); Delves (ed.), Antibody Production: Essential Techniques, John Wiley & Son Ltd (1997); and Kenney, Antibody Solution: An Antibody Methods Manual, Chapman & Hall (1997).

Briefly, such techniques include, *inter alia*, production of monoclonal antibodies by hybridomas and expression of antibodies or fragments or derivatives thereof from host cells engineered to express immunoglobulin genes or fragments thereof. These two methods of production are not mutually exclusive: genes encoding antibodies specific for the polypeptides of the present invention can be cloned from hybridomas and thereafter expressed in other host cells. Nor need the two necessarily be performed together: *e.g.*, genes encoding antibodies specific for the polypeptides of the present invention can be cloned directly from B cells known to be specific for the desired protein, as further described in U.S. Patent No. 5,627,052, the disclosure of which is incorporated herein by reference in its entirety, or from antibody-displaying phage.

Recombinant expression in host cells is particularly useful when fragments or derivatives of the antibodies of the present invention are desired.

Host cells for recombinant antibody production of whole antibodies, antibody fragments, or antibody derivatives can be prokaryotic or eukaryotic.

Prokaryotic hosts are particularly useful for producing phage displayed antibodies of the present invention.

The technology of phage-displayed antibodies, in which antibody variable region fragments are fused, for example, to the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13, is by now well-established.

See, e.g., Sidhu, *Curr. Opin. Biotechnol.* 11(6): 610-6 (2000); Griffiths *et al.*, *Curr. Opin. Biotechnol.* 9(1): 102-8 (1998); Hoogenboom *et al.*, *Immunotechnology*, 4(1): 1-20 (1998); Rader *et al.*, *Current Opinion in Biotechnology* 8: 503-508 (1997); Aujame *et al.*, *Human Antibodies* 8: 155-168 (1997); Hoogenboom, *Trends in Biotechnol.* 15: 62-70 (1997); de Kruif *et al.*, 17: 453-455 (1996); Barbas *et al.*, *Trends in Biotechnol.* 14: 230-234 (1996); Winter *et al.*, *Ann. Rev. Immunol.* 433-455 (1994). Techniques and protocols required to generate, propagate, screen (pan), and use the antibody fragments from such libraries have recently been compiled. See, e.g., Barbas (2001), *supra*; Kay, *supra*; and Abelson, *supra*.

Typically, phage-displayed antibody fragments are scFv fragments or Fab fragments; when desired, full length antibodies can be produced by cloning the variable regions from the displaying phage into a complete antibody and expressing the full length antibody in a further prokaryotic or a eukaryotic host cell. Eukaryotic cells are also useful for expression of the antibodies, antibody fragments, and antibody derivatives of the present invention. For example, antibody fragments of the present invention can be produced in *Pichia pastoris* and in *Saccharomyces cerevisiae*. See, e.g., Takahashi *et al.*, *Biosci. Biotechnol. Biochem.* 64(10): 2138-44 (2000); Freyre *et al.*, *J. Biotechnol.* 76(2-3): 1 57-63 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 117-20 (1999); Pennell *et al.*, *Res. Immunol.* 149(6): 599-603 (1998); Eldin *et al.*, *J. Immunol. Methods*. 201(1): 67-75 (1997);, Frenken *et al.*, *Res. Immunol.* 149(6): 589-99 (1998); and Shusta *et al.*, *Nature Biotechnol.* 16(8): 773-7 (1998).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in insect cells. See, e.g., Li *et al.*, *Protein Expr. Purif.* 21(1): 121-8 (2001); Ailor *et al.*, *Biotechnol. Bioeng.* 58(2-3): 196-203 (1998); Hsu *et al.*, *Biotechnol. Prog.* 13(1): 96-104 (1997); Edelman *et al.*, *Immunology* 91(1): 13-9 (1997); and Nesbit *et al.*, *J. Immunol. Methods* 151(1-2): 201-8 (1992).

Antibodies and fragments and derivatives thereof of the present invention can also be produced in plant cells, particularly maize or tobacco, Giddings *et al.*, *Nature Biotechnol.* 18(11): 1151-5 (2000); Gavilondo *et al.*, *Biotechniques* 29(1): 128-38 (2000); Fischer *et al.*, *J. Biol. Regul. Homeost. Agents* 14(2): 83-92 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 113-6 (1999); Fischer *et al.*, *Biol. Chem.* 380(7-8): 825-39 (1999); Russell, *Curr. Top. Microbiol. Immunol.* 240: 119-38 (1999); and Ma *et al.*, *Plant Physiol.* 109(2): 341-6 (1995).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in transgenic, non-human, mammalian milk. See, e.g. Pollock et al., *J. Immunol Methods.* 231: 147-57 (1999); Young et al., *Res. Immunol.* 149: 609-10 (1998); and Limonta et al., *Immunotechnology* 1: 107-13 (1995).

5 Mammalian cells useful for recombinant expression of antibodies, antibody fragments, and antibody derivatives of the present invention include CHO cells, COS cells, 293 cells, and myeloma cells. Verma et al., *J. Immunol. Methods* 216(1-2):165-81 (1998) review and compare bacterial, yeast, insect and mammalian expression systems for expression of antibodies. Antibodies of the present invention can also be prepared by cell 10 free translation, as further described in Merk et al., *J. Biochem.* (Tokyo) 125(2): 328-33 (1999) and Ryabova et al., *Nature Biotechnol.* 15(1): 79-84 (1997), and in the milk of transgenic animals, as further described in Pollock et al., *J. Immunol. Methods* 231(1-2): 147-57 (1999).

15 The invention further provides antibody fragments that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid 20 molecules of the present invention. Among such useful fragments are Fab, Fab', Fv, F(ab')<sub>2</sub>, and single chain Fv (scFv) fragments. Other useful fragments are described in Hudson, *Curr. Opin. Biotechnol.* 9(4): 395-402 (1998).

The present invention also relates to antibody derivatives that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or 25 the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention.

30 Among such useful derivatives are chimeric, primatized, and humanized antibodies; such derivatives are less immunogenic in human beings, and thus are more suitable for *in vivo* administration, than are unmodified antibodies from non-human mammalian species. Another useful method is PEGylation to increase the serum half life of the antibodies.

Chimeric antibodies typically include heavy and/or light chain variable regions (including both CDR and framework residues) of immunoglobulins of one species, typically mouse, fused to constant regions of another species, typically human. See, e.g., Morrison *et al.*, *Proc. Natl. Acad. Sci USA* 81(21): 6851-5 (1984); Sharon *et al.*, *Nature* 309(5966): 364-7 (1984); Takeda *et al.*, *Nature* 314(6010): 452-4 (1985); and U.S. Patent 5 309(5966): 364-7 (1984); Takeda *et al.*, *Nature* 314(6010): 452-4 (1985); and U.S. Patent No. 5,807,715 the disclosure of which is incorporated herein by reference in its entirety. Primatized and humanized antibodies typically include heavy and/or light chain CDRs from a murine antibody grafted into a non-human primate or human antibody V region framework, usually further comprising a human constant region, Riechmann *et al.*, *Nature* 332(6162): 323-7 (1988); Co *et al.*, *Nature* 351(6326): 501-2 (1991); and U.S. Patent Nos. 10 6,054,297; 5,821,337; 5,770,196; 5,766,886; 5,821,123; 5,869,619; 6,180,377; 6,013,256; 5,693,761; and 6,180,370, the disclosures of which are incorporated herein by reference in their entireties. Other useful antibody derivatives of the invention include heteromeric antibody complexes and antibody fusions, such as diabodies (bispecific antibodies), 15 single-chain diabodies, and intrabodies.

It is contemplated that the nucleic acids encoding the antibodies of the present invention can be operably joined to other nucleic acids forming a recombinant vector for cloning or for expression of the antibodies of the invention. Accordingly, the present invention includes any recombinant vector containing the coding sequences, or part 20 thereof, whether for eukaryotic transduction, transfection or gene therapy. Such vectors may be prepared using conventional molecular biology techniques, known to those with skill in the art, and would comprise DNA encoding sequences for the immunoglobulin V-regions including framework and CDRs or parts thereof, and a suitable promoter either with or without a signal sequence for intracellular transport. Such vectors may be 25 transduced or transfected into eukaryotic cells or used for gene therapy (Marasco *et al.*, *Proc. Natl. Acad. Sci. (USA)* 90: 7889-7893 (1993); Duan *et al.*, *Proc. Natl. Acad. Sci. (USA)* 91: 5075-5079 (1994), by conventional techniques, known to those with skill in the art.

The antibodies of the present invention, including fragments and derivatives 30 thereof, can usefully be labeled. It is, therefore, another aspect of the present invention to provide labeled antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited

by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention. The choice of label depends, in part, upon the desired use.

- For example, when the antibodies of the present invention are used for
- 5 immunohistochemical staining of tissue samples, the label can usefully be an enzyme that catalyzes production and local deposition of a detectable product. Enzymes typically conjugated to antibodies to permit their immunohistochemical visualization are well known, and include alkaline phosphatase,  $\beta$ -galactosidase, glucose oxidase, horseradish peroxidase (HRP), and urease. Typical substrates for production and deposition of
- 10 visually detectable products include o-nitrophenyl-beta-D-galactopyranoside (ONPG); o-phenylenediamine dihydrochloride (OPD); p-nitrophenyl phosphate (PNPP); p-nitrophenyl-beta-D-galactopyranoside (PNPG); 3',3'-diaminobenzidine (DAB); 3-amino-9-ethylcarbazole (AEC); 4-chloro-1-naphthol (CN);
- 5-bromo-4-chloro-3-indolyl-phosphate (BCIP); ABTS®; Bluogal; iodonitrotetrazolium
- 15 (INT); nitroblue tetrazolium chloride (NBT); phenazine methosulfate (PMS); phenolphthalein monophosphate (PMP); tetramethyl benzidine (TMB); tetranitroblue tetrazolium (TNBT); X-Gal; X-Gluc; and X-Glucoside.

Other substrates can be used to produce products for local deposition that are luminescent. For example, in the presence of hydrogen peroxide ( $H_2O_2$ ), horseradish peroxidase (HRP) can catalyze the oxidation of cyclic diacylhydrazides, such as luminol. Immediately following the oxidation, the luminol is in an excited state (intermediate reaction product), which decays to the ground state by emitting light. Strong enhancement of the light emission is produced by enhancers, such as phenolic compounds. Advantages include high sensitivity, high resolution, and rapid detection without radioactivity and requiring only small amounts of antibody. See, e.g., Thorpe *et al.*, *Methods Enzymol.* 133: 331-53 (1986); Kricka *et al.*, *J. Immunoassay* 17(1): 67-83 (1996); and Lundqvist *et al.*, *J. Biolumin. Chemilumin.* 10(6): 353-9 (1995). Kits for such enhanced chemiluminescent detection (ECL) are available commercially. The antibodies can also be labeled using colloidal gold.

30 As another example, when the antibodies of the present invention are used, e.g., for flow cytometric detection, for scanning laser cytometric detection, or for fluorescent immunoassay, they can usefully be labeled with fluorophores. There are a wide variety of fluorophore labels that can usefully be attached to the antibodies of the present invention.

For flow cytometric applications, both for extracellular detection and for intracellular detection, common useful fluorophores can be fluorescein isothiocyanate (FITC), allophycocyanin (APC), R-phycoerythrin (PE), peridinin chlorophyll protein (PerCP), Texas Red, Cy3, Cy5, fluorescence resonance energy tandem fluorophores such as PerCP-Cy5.5, PE-Cy5, PE-Cy5.5, PE-Cy7, PE-Texas Red, and APC-Cy7.

Other fluorophores include, *inter alia*, Alexa Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY 10 R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from 15 Molecular Probes, Inc., Eugene, OR, USA), and Cy2, Cy3, Cy3.5, Cy5, Cy5.5, Cy7, all of which are also useful for fluorescently labeling the antibodies of the present invention. For secondary detection using labeled avidin, streptavidin, captavidin or neutravidin, the antibodies of the present invention can usefully be labeled with biotin.

When the antibodies of the present invention are used, e.g., for western blotting 20 applications, they can usefully be labeled with radioisotopes, such as  $^{33}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^3\text{H}$ , and  $^{125}\text{I}$ . As another example, when the antibodies of the present invention are used for radioimmunotherapy, the label can usefully be  $^{228}\text{Th}$ ,  $^{227}\text{Ac}$ ,  $^{225}\text{Ac}$ ,  $^{223}\text{Ra}$ ,  $^{213}\text{Bi}$ ,  $^{212}\text{Pb}$ ,  $^{212}\text{Bi}$ ,  $^{211}\text{At}$ ,  $^{203}\text{Pb}$ ,  $^{194}\text{Os}$ ,  $^{188}\text{Re}$ ,  $^{186}\text{Re}$ ,  $^{153}\text{Sm}$ ,  $^{149}\text{Tb}$ ,  $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{111}\text{In}$ ,  $^{105}\text{Rh}$ ,  $^{99m}\text{Tc}$ ,  $^{97}\text{Ru}$ ,  $^{90}\text{Y}$ ,  $^{90}\text{Sr}$ ,  $^{88}\text{Y}$ ,  $^{72}\text{Se}$ ,  $^{67}\text{Cu}$ , or  $^{47}\text{Sc}$ .

As another example, when the antibodies of the present invention are to be used 25 for *in vivo* diagnostic use, they can be rendered detectable by conjugation to MRI contrast agents, such as gadolinium diethylenetriaminepentaacetic acid (DTPA), Lauffer *et al.*, *Radiology* 207(2): 529-38 (1998), or by radioisotopic labeling.

As would be understood, use of the labels described above is not restricted to the 30 application as for which they were mentioned.

The antibodies of the present invention, including fragments and derivatives thereof, can also be conjugated to toxins, in order to target the toxin's ablative action to cells that display and/or express the polypeptides of the present invention. Commonly, the

antibody in such immunotoxins is conjugated to Pseudomonas exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin lethal factor, or ricin. See Hall (ed.), Immunotoxin Methods and Protocols (Methods in Molecular Biology, vol. 166), Humana Press (2000); and Frankel *et al.* (eds.), Clinical Applications of Immunotoxins, Springer-Verlag (1998).

5       The antibodies of the present invention can usefully be attached to a substrate, and it is, therefore, another aspect of the invention to provide antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of  
10      the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, attached to a substrate. Substrates can be porous or nonporous, planar or nonplanar. For example, the antibodies of the present invention can usefully be conjugated to filtration media, such as NHS-activated Sepharose or CNBr-activated Sepharose for purposes of immunoaffinity chromatography. For example, the  
15      antibodies of the present invention can usefully be attached to paramagnetic microspheres, typically by biotin-streptavidin interaction, which microsphere can then be used for isolation of cells that express or display the polypeptides of the present invention. As another example, the antibodies of the present invention can usefully be attached to the surface of a microtiter plate for ELISA.

20       As noted above, the antibodies of the present invention can be produced in prokaryotic and eukaryotic cells. It is, therefore, another aspect of the present invention to provide cells that express the antibodies of the present invention, including hybridoma cells, B cells, plasma cells, and host cells recombinantly modified to express the antibodies of the present invention.

25       In yet a further aspect, the present invention provides aptamers evolved to bind specifically to one or more of the BSPs of the present invention or to polypeptides encoded by the BSNAAs of the invention.

30       In sum, one of skill in the art, provided with the teachings of this invention, has available a variety of methods which may be used to alter the biological properties of the antibodies of this invention including methods which would increase or decrease the stability or half-life, immunogenicity, toxicity, affinity or yield of a given antibody molecule, or to alter it in any other way that may render it more suitable for a particular application.

Transgenic Animals and Cells

In another aspect, the invention provides transgenic cells and non-human organisms comprising nucleic acid molecules of the invention. In a preferred embodiment, the transgenic cells and non-human organisms comprise a nucleic acid molecule encoding a BSP. In a preferred embodiment, the BSP comprises an amino acid sequence selected from SEQ ID NO: 95-156, or a fragment, mutein, homologous protein or allelic variant thereof. In another preferred embodiment, the transgenic cells and non-human organism comprise a BSNA of the invention, preferably a BSNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-94, or a part, substantially similar nucleic acid molecule, allelic variant or hybridizing nucleic acid molecule thereof.

In another embodiment, the transgenic cells and non-human organisms have a targeted disruption or replacement of the endogenous orthologue of the human BSG. The transgenic cells can be embryonic stem cells or somatic cells. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. Methods of producing transgenic animals are well known in the art. *See, e.g., Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual*, 2d ed., Cold Spring Harbor Press (1999); Jackson *et al.*, *Mouse Genetics and Transgenics: A Practical Approach*, Oxford University Press (2000); and Pinkert, *Transgenic Animal Technology: A Laboratory Handbook*, Academic Press (1999).

Any technique known in the art may be used to introduce a nucleic acid molecule of the invention into an animal to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection. (*see, e.g., Paterson et al., Appl. Microbiol. Biotechnol. 40: 691-698 (1994); Carver et al., Biotechnology 11: 25 1263-1270 (1993); Wright et al., Biotechnology 9: 830-834 (1991); and U.S. Patent No. 4,873,191, herein incorporated by reference in its entirety*); retrovirus-mediated gene transfer into germ lines, blastocysts or embryos (*see, e.g., Van der Putten et al., Proc. Natl. Acad. Sci., USA 82: 6148-6152 (1985)*); gene targeting in embryonic stem cells (*see, e.g., Thompson et al., Cell 56: 313-321 (1989)*); electroporation of cells or embryos (*see, e.g., Lo, 1983, Mol. Cell. Biol. 3: 1803-1814 (1983)*); introduction using a gene gun (*see, e.g., Ulmer et al., Science 259: 1745-49 (1993)*); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (*see, e.g., Lavitano et al., Cell 57: 717-723 (1989)*)).

Other techniques include, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (*see, e.g.,* Campell *et al.*, *Nature* 380: 64-66 (1996); Wilmut *et al.*, *Nature* 385: 810-813 (1997)). The present invention provides for transgenic animals that carry the transgene (*i.e.*, a nucleic acid molecule of the invention) in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e. e.*, mosaic animals or chimeric animals.

The transgene may be integrated as a single transgene or as multiple copies, such as in concatamers, *e. g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, 10 *e.g.*, the teaching of Lasko *et al. et al.*, *Proc. Natl. Acad. Sci. USA* 89: 6232- 6236 (1992). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished 15 by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (RT-PCR). 20 Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding 25 strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to 30 both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions  
5 and/or disorders.

Methods for creating a transgenic animal with a disruption of a targeted gene are also well known in the art. In general, a vector is designed to comprise some nucleotide sequences homologous to the endogenous targeted gene. The vector is introduced into a cell so that it may integrate, via homologous recombination with chromosomal sequences,  
10 into the endogenous gene, thereby disrupting the function of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type. *See, e.g., Gu et al., Science 265: 103-106 (1994).* The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the  
15 art. *See, e.g., Smithies et al., Nature 317: 230-234 (1985); Thomas et al., Cell 51: 503-512 (1987); Thompson et al., Cell 5: 313-321 (1989).*

In one embodiment, a mutant, non-functional nucleic acid molecule of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous nucleic acid sequence (either the coding regions or regulatory regions of the  
20 gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfet cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such  
25 approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene. *See, e.g., Thomas, supra and Thompson, supra.* However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that  
30 will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.,* knockouts) are administered to a

patient in vivo. Such cells may be obtained from an animal or patient or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. *See, e.g.*, U.S. Patent Nos. 5,399,349 and 5,460,959, each of which is incorporated by reference herein in its entirety.

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Computer Readable Means

A further aspect of the invention is a computer readable means for storing the nucleic acid and amino acid sequences of the instant invention. In a preferred embodiment, the invention provides a computer readable means for storing SEQ ID NO: 5 95-156 and SEQ ID NO: 1-94 as described herein, as the complete set of sequences or in any combination. The records of the computer readable means can be accessed for reading and display and for interface with a computer system for the application of programs allowing for the location of data upon a query for data meeting certain criteria, the comparison of sequences, the alignment or ordering of sequences meeting a set of 10 criteria, and the like.

The nucleic acid and amino acid sequences of the invention are particularly useful as components in databases useful for search analyses as well as in sequence analysis algorithms. As used herein, the terms "nucleic acid sequences of the invention" and "amino acid sequences of the invention" mean any detectable chemical or physical 15 characteristic of a polynucleotide or polypeptide of the invention that is or may be reduced to or stored in a computer readable form. These include, without limitation, chromatographic scan data or peak data, photographic data or scan data therefrom, and mass spectrographic data.

This invention provides computer readable media having stored thereon sequences 20 of the invention. A computer readable medium may comprise one or more of the following: a nucleic acid sequence comprising a sequence of a nucleic acid sequence of the invention; an amino acid sequence comprising an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences 25 wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of one or more nucleic acid sequences of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said 30 sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of a nucleic acid sequence of the invention; a data set

representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention. The computer readable medium can be any composition of matter used to store information or data, including, for example, commercially available floppy disks, tapes, hard drives, compact disks, and video disks.

5       Also provided by the invention are methods for the analysis of character sequences, particularly genetic sequences. Preferred methods of sequence analysis include, for example, methods of sequence homology analysis, such as identity and similarity analysis, RNA structure analysis, sequence assembly, cladistic analysis, sequence motif analysis, open reading frame determination, nucleic acid base calling, and 10 sequencing chromatogram peak analysis.

A computer-based method is provided for performing nucleic acid sequence identity or similarity identification. This method comprises the steps of providing a nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and comparing said nucleic acid sequence to at least one 15 nucleic acid or amino acid sequence to identify sequence identity or similarity.

A computer-based method is also provided for performing amino acid homology identification, said method comprising the steps of: providing an amino acid sequence comprising the sequence of an amino acid of the invention in a computer readable medium; and comparing said amino acid sequence to at least one nucleic acid or an amino 20 acid sequence to identify homology.

A computer-based method is still further provided for assembly of overlapping nucleic acid sequences into a single nucleic acid sequence, said method comprising the steps of: providing a first nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and screening for at least one 25 overlapping region between said first nucleic acid sequence and a second nucleic acid sequence. In addition, the invention includes a method of using patterns of expression associated with either the nucleic acids or proteins in a computer-based method to diagnose disease.

#### Diagnostic Methods for breast Cancer

30       The present invention also relates to quantitative and qualitative diagnostic assays and methods for detecting, diagnosing, monitoring, staging and predicting cancers by comparing expression of a BSNA or a BSP in a human patient that has or may have breast

cancer, or who is at risk of developing breast cancer, with the expression of a BSNA or a BSP in a normal human control. For purposes of the present invention, "expression of a BSNA" or "BSNA expression" means the quantity of BSNA mRNA that can be measured by any method known in the art or the level of transcription that can be measured by any method known in the art in a cell, tissue, organ or whole patient. Similarly, the term "expression of a BSP" or "BSP expression" means the amount of BSP that can be measured by any method known in the art or the level of translation of a BSNA that can be measured by any method known in the art.

The present invention provides methods for diagnosing breast cancer in a patient, 10 by analyzing for changes in levels of BSNA or BSP in cells, tissues, organs or bodily fluids compared with levels of BSNA or BSP in cells, tissues, organs or bodily fluids of preferably the same type from a normal human control, wherein an increase, or decrease in certain cases, in levels of a BSNA or BSP in the patient versus the normal human control is associated with the presence of breast cancer or with a predilection to the disease. In 15 another preferred embodiment, the present invention provides methods for diagnosing breast cancer in a patient by analyzing changes in the structure of the mRNA of a BSG compared to the mRNA from a normal control. These changes include, without limitation, aberrant splicing, alterations in polyadenylation and/or alterations in 5' nucleotide capping. In yet another preferred embodiment, the present invention provides methods for 20 diagnosing breast cancer in a patient by analyzing changes in a BSP compared to a BSP from a normal patient. These changes include, e.g., alterations, including post translational modifications such as glycosylation and/or phosphorylation of the BSP or changes in the subcellular BSP localization.

For purposes of the present invention, diagnosing means that BSNA or BSP levels 25 are used to determine the presence or absence of disease in a patient. As will be understood by those of skill in the art, measurement of other diagnostic parameters may be required for definitive diagnosis or determination of the appropriate treatment for the disease. The determination may be made by a clinician, a doctor, a testing laboratory, or a patient using an over the counter test. The patient may have symptoms of disease or may 30 be asymptomatic. In addition, the BSNA or BSP levels of the present invention may be used as screening marker to determine whether further tests or biopsies are warranted. In addition, the BSNA or BSP levels may be used to determine the vulnerability or susceptibility to disease.

In a preferred embodiment, the expression of a BSNA is measured by determining the amount of a mRNA that encodes an amino acid sequence selected from SEQ ID NO: 95-156, a homolog, an allelic variant, or a fragment thereof. In a more preferred embodiment, the BSNA expression that is measured is the level of expression of a BSNA mRNA selected from SEQ ID NO: 1-94, or a hybridizing nucleic acid, homologous nucleic acid or allelic variant thereof, or a part of any of these nucleic acid molecules.

5 BSNA expression may be measured by any method known in the art, such as those described *supra*, including measuring mRNA expression by Northern blot, quantitative or qualitative reverse transcriptase PCR (RT-PCR), microarray, dot or slot blots or *in situ* hybridization. *See, e.g.,* Ausubel (1992), *supra*; Ausubel (1999), *supra*; Sambrook (1989), *supra*; and Sambrook (2001), *supra*. BSNA transcription may be measured by any method known in the art including using a reporter gene hooked up to the promoter of a BSG of interest or doing nuclear run-off assays. Alterations in mRNA structure, *e.g.*, aberrant splicing variants, may be determined by any method known in the art, including,

10 15 RT-PCR followed by sequencing or restriction analysis. As necessary, BSNA expression may be compared to a known control, such as normal breast nucleic acid, to detect a change in expression.

In another preferred embodiment, the expression of a BSP is measured by determining the level of a BSP having an amino acid sequence selected from the group consisting of SEQ ID NO: 95-156, a homolog, an allelic variant, or a fragment thereof. Such levels are preferably determined in at least one of cells, tissues, organs and/or bodily fluids, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for diagnosing over- or underexpression of a BSNA or BSP compared to normal control bodily fluids, cells, or tissue samples may be used to diagnose the presence of breast cancer. The expression level of a BSP may be determined by any method known in the art, such as those described *supra*. In a preferred embodiment, the BSP expression level may be determined by radioimmunoassays, competitive-binding assays, ELISA, Western blot, FACS, immunohistochemistry, immunoprecipitation, proteomic approaches: two-dimensional gel electrophoresis (2D electrophoresis) and non-gel-based approaches such as mass spectrometry or protein interaction profiling. *See, e.g.,* Harlow (1999), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. Alterations in the BSP structure may be determined by any method known in the art, including, *e.g.*, using antibodies that specifically recognize phosphoserine,

phosphothreonine or phosphotyrosine residues, two-dimensional polyacrylamide gel electrophoresis (2D PAGE) and/or chemical analysis of amino acid residues of the protein.  
*Id.*

In a preferred embodiment, a radioimmunoassay (RIA) or an ELISA is used. An 5 antibody specific to a BSP is prepared if one is not already available. In a preferred embodiment, the antibody is a monoclonal antibody. The anti-BSP antibody is bound to a solid support and any free protein binding sites on the solid support are blocked with a protein such as bovine serum albumin. A sample of interest is incubated with the antibody on the solid support under conditions in which the BSP will bind to the anti-BSP antibody. 10 The sample is removed, the solid support is washed to remove unbound material, and an anti-BSP antibody that is linked to a detectable reagent (a radioactive substance for RIA and an enzyme for ELISA) is added to the solid support and incubated under conditions in which binding of the BSP to the labeled antibody will occur. After binding, the unbound labeled antibody is removed by washing. For an ELISA, one or more substrates are added 15 to produce a colored reaction product that is based upon the amount of an BSP in the sample. For an RIA, the solid support is counted for radioactive decay signals by any method known in the art. Quantitative results for both RIA and ELISA typically are obtained by reference to a standard curve.

Other methods to measure BSP levels are known in the art. For instance, a 20 competition assay may be employed wherein an anti-BSP antibody is attached to a solid support and an allocated amount of a labeled BSP and a sample of interest are incubated with the solid support. The amount of labeled BSP attached to the solid support can be correlated to the quantity of a BSP in the sample.

Of the proteomic approaches, 2D PAGE is a well known technique. Isolation of 25 individual proteins from a sample such as serum is accomplished using sequential separation of proteins by isoelectric point and molecular weight. Typically, polypeptides are first separated by isoelectric point (the first dimension) and then separated by size using an electric current (the second dimension). In general, the second dimension is perpendicular to the first dimension. Because no two proteins with different sequences are 30 identical on the basis of both size and charge, the result of 2D PAGE is a roughly square gel in which each protein occupies a unique spot. Analysis of the spots with chemical or antibody probes, or subsequent protein microsequencing can reveal the relative abundance of a given protein and the identity of the proteins in the sample.

- Expression levels of a BSNA can be determined by any method known in the art, including PCR and other nucleic acid methods, such as ligase chain reaction (LCR) and nucleic acid sequence based amplification (NASBA), can be used to detect malignant cells for diagnosis and monitoring of various malignancies. For example, reverse-transcriptase
- 5 PCR (RT-PCR) is a powerful technique which can be used to detect the presence of a specific mRNA population in a complex mixture of thousands of other mRNA species. In RT-PCR, an mRNA species is first reverse transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase; the cDNA is then amplified as in a standard PCR reaction.
- 10 Hybridization to specific DNA molecules (*e.g.*, oligonucleotides) arrayed on a solid support can be used to both detect the expression of and quantitate the level of expression of one or more BSNAAs of interest. In this approach, all or a portion of one or more BSNAAs is fixed to a substrate. A sample of interest, which may comprise RNA, *e.g.*, total RNA or polyA-selected mRNA, or a complementary DNA (cDNA) copy of the RNA
- 15 is incubated with the solid support under conditions in which hybridization will occur between the DNA on the solid support and the nucleic acid molecules in the sample of interest. Hybridization between the substrate-bound DNA and the nucleic acid molecules in the sample can be detected and quantitated by several means, including, without limitation, radioactive labeling or fluorescent labeling of the nucleic acid molecule or a
- 20 secondary molecule designed to detect the hybrid.

The above tests can be carried out on samples derived from a variety of cells, bodily fluids and/or tissue extracts such as homogenates or solubilized tissue obtained from a patient. Tissue extracts are obtained routinely from tissue biopsy and autopsy material. Bodily fluids useful in the present invention include blood, urine, saliva or any

25 other bodily secretion or derivative thereof. As used herein "blood" includes whole blood, plasma, serum, circulating epithelial cells, constituents, or any derivative of blood.

In addition to detection in bodily fluids, the proteins and nucleic acids of the invention are suitable to detection by cell capture technology. Whole cells may be captured by a variety methods for example magnetic separation, U.S. Patent Nos.

30 5,200,084; 5,186,827; 5,108,933; 4,925,788, the disclosures of which are incorporated herein by reference in their entireties. Epithelial cells may be captured using such products as Dynabeads® or CELLlection™ (Dynal Biotech, Oslo, Norway). Alternatively, fractions of blood may be captured, *e.g.*, the buffy coat fraction (50mm cells isolated from

5ml of blood) containing epithelial cells. In addition, cancer cells may be captured using the techniques described in WO 00/47998, the disclosure of which is incorporated herein by reference in its entirety. Once the cells are captured or concentrated, the proteins or nucleic acids are detected by the means described in the subject application. Alternatively, 5 nucleic acids may be captured directly from blood samples, see U.S. Patent Nos. 6,156,504, 5,501,963; or WO 01/42504 , the disclosures of which are incorporated herein by reference in their entireties.

In a preferred embodiment, the specimen tested for expression of BSNA or BSP includes without limitation breast tissue, breast cells grown in cell culture, blood, serum, 10 lymph node tissue, and lymphatic fluid. In another preferred embodiment, especially when metastasis of a primary breast cancer is known or suspected, specimens include, without limitation, tissues from brain, bone, bone marrow, liver, lungs, colon, and adrenal glands. In general, the tissues may be sampled by biopsy, including, without limitation, needle biopsy, e.g., transthoracic needle aspiration, cervical mediastinoscopy, endoscopic 15 lymph node biopsy, video-assisted thoracoscopy, exploratory thoracotomy, bone marrow biopsy and bone marrow aspiration.

All the methods of the present invention may optionally include determining the expression levels of one or more other cancer markers in addition to determining the expression level of a BSNA or BSP. In many cases, the use of another cancer marker will 20 decrease the likelihood of false positives or false negatives. In one embodiment, the one or more other cancer markers include other BSNA or BSPs as disclosed herein. Other cancer markers useful in the present invention will depend on the cancer being tested and are known to those of skill in the art. In a preferred embodiment, at least one other cancer marker in addition to a particular BSNA or BSP is measured. In a more preferred 25 embodiment, at least two other additional cancer markers are used. In an even more preferred embodiment, at least three, more preferably at least five, even more preferably at least ten additional cancer markers are used.

#### *Diagnosing*

In one aspect, the invention provides a method for determining the expression 30 levels and/or structural alterations of one or more BSNA and/or BSP in a sample from a patient suspected of having breast cancer. In general, the method comprises the steps of obtaining the sample from the patient, determining the expression level or structural alterations of a BSNA and/or BSP and then ascertaining whether the patient has breast

cancer from the expression level of the BSNA or BSP. In general, if high expression relative to a control of a BSNA or BSP is indicative of breast cancer, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of breast cancer, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

The present invention also provides a method of determining whether breast cancer has metastasized in a patient. One may identify whether the breast cancer has metastasized by measuring the expression levels and/or structural alterations of one or more BSNAAs and/or BSPs in a variety of tissues. The presence of a BSNA or BSP in a certain tissue at levels higher than that of corresponding noncancerous tissue (e.g., the same tissue from another individual) is indicative of metastasis if high level expression of a BSNA or BSP is associated with breast cancer. Similarly, the presence of a BSNA or BSP in a tissue at levels lower than that of corresponding noncancerous tissue is indicative of metastasis if low level expression of a BSNA or BSP is associated with breast cancer. Further, the presence of a structurally altered BSNA or BSP that is associated with breast cancer is also indicative of metastasis.

In general, if high expression relative to a control of a BSNA or BSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the BSNA or BSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the BSNA or BSP is at least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten

times lower than in preferably the same cells, tissues or bodily fluid of a normal human control.

#### *Staging*

The invention also provides a method of staging breast cancer in a human patient.

- 5      The method comprises identifying a human patient having breast cancer and analyzing cells, tissues or bodily fluids from such human patient for expression levels and/or structural alterations of one or more BSNA<sub>s</sub> or BSP<sub>s</sub>. First, one or more tumors from a variety of patients are staged according to procedures well known in the art, and the expression levels of one or more BSNA<sub>s</sub> or BSP<sub>s</sub> is determined for each stage to obtain a
- 10     standard expression level for each BSNA and BSP. Then, the BSNA or BSP expression levels of the BSNA or BSP are determined in a biological sample from a patient whose stage of cancer is not known. The BSNA or BSP expression levels from the patient are then compared to the standard expression level. By comparing the expression level of the BSNA<sub>s</sub> and BSP<sub>s</sub> from the patient to the standard expression levels, one may determine
- 15     the stage of the tumor. The same procedure may be followed using structural alterations of a BSNA or BSP to determine the stage of a breast cancer.

#### *Monitoring*

- Further provided is a method of monitoring breast cancer in a human patient. One may monitor a human patient to determine whether there has been metastasis and, if there has been, when metastasis began to occur. One may also monitor a human patient to determine whether a preneoplastic lesion has become cancerous. One may also monitor a human patient to determine whether a therapy, e.g., chemotherapy, radiotherapy or surgery, has decreased or eliminated the breast cancer. The monitoring may determine if there has been a reoccurrence and, if so, determine its nature. The method comprises
- 20     identifying a human patient that one wants to monitor for breast cancer, periodically analyzing cells, tissues or bodily fluids from such human patient for expression levels of one or more BSNA<sub>s</sub> or BSP<sub>s</sub>, and comparing the BSNA or BSP levels over time to those BSNA or BSP expression levels obtained previously. Patients may also be monitored by measuring one or more structural alterations in a BSNA or BSP that are associated with
  - 25     breast cancer.

If increased expression of a BSNA or BSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting an

increase in the expression level of a BSNA or BSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. One having ordinary skill in the art would recognize that if this were the case, then a decreased expression level would be indicative of no metastasis, effective therapy or failure to progress to a neoplastic lesion. If decreased expression of a BSNA or BSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting a decrease in the expression level of a BSNA or BSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. In a preferred embodiment, the levels of BSNAs or BSPs are determined from the same cell type, tissue or bodily fluid as prior patient samples. Monitoring a patient for onset of breast cancer metastasis is periodic and preferably is done on a quarterly basis, but may be done more or less frequently.

The methods described herein can further be utilized as prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with increased or decreased expression levels of a BSNA and/or BSP. The present invention provides a method in which a test sample is obtained from a human patient and one or more BSNAs and/or BSPs are detected. The presence of higher (or lower) BSNA or BSP levels as compared to normal human controls is diagnostic for the human patient being at risk for developing cancer, particularly breast cancer. The effectiveness of therapeutic agents to decrease (or increase) expression or activity of one or more BSNAs and/or BSPs of the invention can also be monitored by analyzing levels of expression of the BSNAs and/or BSPs in a human patient in clinical trials or in *in vitro* screening assays such as in human cells. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the human patient or cells, as the case may be, to the agent being tested.

#### *Detection of Genetic Lesions or Mutations*

The methods of the present invention can also be used to detect genetic lesions or mutations in a BSG, thereby determining if a human with the genetic lesion is susceptible to developing breast cancer or to determine what genetic lesions are responsible, or are partly responsible, for a person's existing breast cancer. Genetic lesions can be detected, for example, by ascertaining the existence of a deletion, insertion and/or substitution of one or more nucleotides from the BSGs of this invention, a chromosomal rearrangement

of a BSG, an aberrant modification of a BSG (such as of the methylation pattern of the genomic DNA), or allelic loss of a BSG. Methods to detect such lesions in the BSG of this invention are known to those having ordinary skill in the art following the teachings of the specification.

5    Methods of Detecting Noncancerous breast Diseases

The present invention also provides methods for determining the expression levels and/or structural alterations of one or more BSNA and/or BSPs in a sample from a patient suspected of having or known to have a noncancerous breast disease. In general, the method comprises the steps of obtaining a sample from the patient, determining the  
10 expression level or structural alterations of a BSNA and/or BSP, comparing the expression level or structural alteration of the BSNA or BSP to a normal breast control, and then ascertaining whether the patient has a noncancerous breast disease. In general, if high expression relative to a control of a BSNA or BSP is indicative of a particular noncancerous breast disease, a diagnostic assay is considered positive if the level of  
15 expression of the BSNA or BSP is at least two times higher, and more preferably are at least five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of a noncancerous breast disease, a diagnostic assay is considered positive if the level of expression of the BSNA or  
20 BSP is at least two times lower, more preferably are at least five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

One having ordinary skill in the art may determine whether a BSNA and/or BSP is  
25 associated with a particular noncancerous breast disease by obtaining breast tissue from a patient having a noncancerous breast disease of interest and determining which BSNA and/or BSPs are expressed in the tissue at either a higher or a lower level than in normal breast tissue. In another embodiment, one may determine whether a BSNA or BSP exhibits structural alterations in a particular noncancerous breast disease state by obtaining  
30 breast tissue from a patient having a noncancerous breast disease of interest and determining the structural alterations in one or more BSNA and/or BSPs relative to normal breast tissue.

Methods for Identifying breast Tissue

In another aspect, the invention provides methods for identifying breast tissue. These methods are particularly useful in, *e.g.*, forensic science, breast cell differentiation and development, and in tissue engineering.

- 5        In one embodiment, the invention provides a method for determining whether a sample is breast tissue or has breast tissue-like characteristics. The method comprises the steps of providing a sample suspected of comprising breast tissue or having breast tissue-like characteristics, determining whether the sample expresses one or more BSNA and/or BSPs, and, if the sample expresses one or more BSNA and/or BSPs, concluding that the
- 10      sample comprises breast tissue. In a preferred embodiment, the BSNA encodes a polypeptide having an amino acid sequence selected from SEQ ID NO: 95-156, or a homolog, allelic variant or fragment thereof. In a more preferred embodiment, the BSNA has a nucleotide sequence selected from SEQ ID NO: 1-94, or a hybridizing nucleic acid, an allelic variant or a part thereof. Determining whether a sample expresses a BSNA can be accomplished by any method known in the art. Preferred methods include hybridization to microarrays, Northern blot hybridization, and quantitative or qualitative RT-PCR. In another preferred embodiment, the method can be practiced by determining whether a BSP is expressed. Determining whether a sample expresses a BSP can be accomplished by any method known in the art. Preferred methods include Western blot,
- 15      ELISA, RIA and 2D PAGE. In one embodiment, the BSP has an amino acid sequence selected from SEQ ID NO: 95-156, or a homolog, allelic variant or fragment thereof. In another preferred embodiment, the expression of at least two BSNA and/or BSPs is determined. In a more preferred embodiment, the expression of at least three, more preferably four and even more preferably five BSNA and/or BSPs are determined.
- 20      In one embodiment, the method can be used to determine whether an unknown tissue is breast tissue. This is particularly useful in forensic science, in which small, damaged pieces of tissues that are not identifiable by microscopic or other means are recovered from a crime or accident scene. In another embodiment, the method can be used to determine whether a tissue is differentiating or developing into breast tissue. This
- 25      is important in monitoring the effects of the addition of various agents to cell or tissue culture, *e.g.*, in producing new breast tissue by tissue engineering. These agents include, *e.g.*, growth and differentiation factors, extracellular matrix proteins and culture medium. Other factors that may be measured for effects on tissue development and differentiation

include gene transfer into the cells or tissues, alterations in pH, aqueous:air interface and various other culture conditions.

Methods for Producing and Modifying breast Tissue

In another aspect, the invention provides methods for producing engineered breast tissue or cells. In one embodiment, the method comprises the steps of providing cells, introducing a BSNA or a BSG into the cells, and growing the cells under conditions in which they exhibit one or more properties of breast tissue cells. In a preferred embodiment, the cells are pluripotent. As is well known in the art, normal breast tissue comprises a large number of different cell types. Thus, in one embodiment, the 10 engineered breast tissue or cells comprises one of these cell types. In another embodiment, the engineered breast tissue or cells comprises more than one breast cell type. Further, the culture conditions of the cells or tissue may require manipulation in order to achieve full differentiation and development of the breast cell tissue. Methods for manipulating culture conditions are well known in the art.

15 Nucleic acid molecules encoding one or more BSPs are introduced into cells, preferably pluripotent cells. In a preferred embodiment, the nucleic acid molecules encode BSPs having amino acid sequences selected from SEQ ID NO: 95-156, or homologous proteins, analogs, allelic variants or fragments thereof. In a more preferred embodiment, the nucleic acid molecules have a nucleotide sequence selected from SEQ ID NO: 1-94, or hybridizing nucleic acids, allelic variants or parts thereof. In another highly preferred embodiment, a BSG is introduced into the cells. Expression vectors and methods of introducing nucleic acid molecules into cells are well known in the art and are described in detail, *supra*.

20 Artificial breast tissue may be used to treat patients who have lost some or all of their breast function.

Pharmaceutical Compositions

In another aspect, the invention provides pharmaceutical compositions comprising the nucleic acid molecules, polypeptides, fusion proteins, antibodies, antibody derivatives, antibody fragments, agonists, antagonists, or inhibitors of the present invention. In a 30 preferred embodiment, the pharmaceutical composition comprises a BSNA or part thereof. In a more preferred embodiment, the BSNA has a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-94, a nucleic acid that hybridizes thereto, an allelic

variant thereof, or a nucleic acid that has substantial sequence identity thereto. In another preferred embodiment, the pharmaceutical composition comprises a BSP or fragment thereof. In a more preferred embodiment, the pharmaceutical composition comprises a BSP having an amino acid sequence that is selected from the group consisting of SEQ ID NO: 95-156, a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof. In another preferred embodiment, the pharmaceutical composition comprises an anti-BSP antibody, preferably an antibody that specifically binds to a BSP having an amino acid that is selected from the group consisting of SEQ ID NO: 95-156, or an antibody that binds to a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof.

Such a composition typically contains from about 0.1 to 90% by weight of a therapeutic agent of the invention formulated in and/or with a pharmaceutically acceptable carrier or excipient.

Pharmaceutical formulation is a well-established art that is further described in Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20<sup>th</sup> ed., Lippincott, Williams & Wilkins (2000); Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7<sup>th</sup> ed., Lippincott Williams & Wilkins (1999); and Kibbe (ed.), Handbook of Pharmaceutical Excipients American Pharmaceutical Association, 3<sup>rd</sup> ed. (2000) and thus need not be described in detail herein.

Briefly, formulation of the pharmaceutical compositions of the present invention will depend upon the route chosen for administration. The pharmaceutical compositions utilized in this invention can be administered by various routes including both enteral and parenteral routes, including oral, intravenous, intramuscular, subcutaneous, inhalation, topical, sublingual, rectal, intra-arterial, intramedullary, intrathecal, intraventricular, transmucosal, transdermal, intranasal, intraperitoneal, intrapulmonary, and intrauterine.

Oral dosage forms can be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Solid formulations of the compositions for oral administration can contain suitable carriers or excipients, such as carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or microcrystalline cellulose; gums including arabic and

tragacanth; proteins such as gelatin and collagen; inorganics, such as kaolin, calcium carbonate, dicalcium phosphate, sodium chloride; and other agents such as acacia and alginic acid.

Agents that facilitate disintegration and/or solubilization can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate, microcrystalline cellulose, cornstarch, sodium starch glycolate, and alginic acid.

Tablet binders that can be used include acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone<sup>TM</sup>), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

10 Lubricants that can be used include magnesium stearates, stearic acid, silicone fluid, talc, waxes, oils, and colloidal silica.

Fillers, agents that facilitate disintegration and/or solubilization, tablet binders and lubricants, including the aforementioned, can be used singly or in combination.

15 Solid oral dosage forms need not be uniform throughout. For example, dragee cores can be used in conjunction with suitable coatings, such as concentrated sugar solutions, which can also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

20 Oral dosage forms of the present invention include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without 25 stabilizers.

Additionally, dyestuffs or pigments can be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, *i.e.*, dosage.

30 Liquid formulations of the pharmaceutical compositions for oral (enteral) administration are prepared in water or other aqueous vehicles and can contain various suspending agents such as methylcellulose, alginates, tragacanth, pectin, kelgin, carrageenan, acacia, polyvinylpyrrolidone, and polyvinyl alcohol. The liquid formulations can also include solutions, emulsions, syrups and elixirs containing, together with the active compound(s), wetting agents, sweeteners, and coloring and flavoring agents.

The pharmaceutical compositions of the present invention can also be formulated for parenteral administration. Formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions.

For intravenous injection, water soluble versions of the compounds of the present invention are formulated in, or if provided as a lyophilate, mixed with, a physiologically acceptable fluid vehicle, such as 5% dextrose ("D5"), physiologically buffered saline, 0.9% saline, Hanks' solution, or Ringer's solution. Intravenous formulations may include carriers, excipients or stabilizers including, without limitation, calcium, human serum albumin, citrate, acetate, calcium chloride, carbonate, and other salts.

Intramuscular preparations, *e.g.* a sterile formulation of a suitable soluble salt form of the compounds of the present invention, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution. Alternatively, a suitable insoluble form of the compound can be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, such as an ester of a long chain fatty acid (*e.g.*, ethyl oleate), fatty oils such as sesame oil, triglycerides, or liposomes.

Parenteral formulations of the compositions can contain various carriers such as vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like).

Aqueous injection suspensions can also contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Non-lipid polycationic amino polymers can also be used for delivery. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical compositions of the present invention can also be formulated to permit injectable, long-term, deposition. Injectable depot forms may be made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in microemulsions that are compatible with body tissues.

The pharmaceutical compositions of the present invention can be administered topically. For topical use the compounds of the present invention can also be prepared in suitable forms to be applied to the skin, or mucus membranes of the nose and throat, and can take the form of lotions, creams, ointments, liquid sprays or inhalants, drops, tinctures, 5 lozenges, or throat paints. Such topical formulations further can include chemical compounds such as dimethylsulfoxide (DMSO) to facilitate surface penetration of the active ingredient. In other transdermal formulations, typically in patch-delivered formulations, the pharmaceutically active compound is formulated with one or more skin penetrants, such as 2-N-methyl-pyrrolidone (NMP) or Azone. A topical semi-solid 10 ointment formulation typically contains a concentration of the active ingredient from about 1 to 20%, e.g., 5 to 10%, in a carrier such as a pharmaceutical cream base.

For application to the eyes or ears, the compounds of the present invention can be presented in liquid or semi-liquid form formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

15 For rectal administration the compounds of the present invention can be administered in the form of suppositories admixed with conventional carriers such as cocoa butter, wax or other glyceride.

Inhalation formulations can also readily be formulated. For inhalation, various powder and liquid formulations can be prepared. For aerosol preparations, a sterile 20 formulation of the compound or salt form of the compound may be used in inhalers, such as metered dose inhalers, and nebulizers. Aerosolized forms may be especially useful for treating respiratory disorders.

25 Alternatively, the compounds of the present invention can be in powder form for reconstitution in the appropriate pharmaceutically acceptable carrier at the time of delivery.

The pharmaceutically active compound in the pharmaceutical compositions of the present invention can be provided as the salt of a variety of acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base 30 forms.

After pharmaceutical compositions have been prepared, they are packaged in an appropriate container and labeled for treatment of an indicated condition.

The active compound will be present in an amount effective to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

A "therapeutically effective dose" refers to that amount of active ingredient, for example BSP polypeptide, fusion protein, or fragments thereof, antibodies specific for BSP, agonists, antagonists or inhibitors of BSP, which ameliorates the signs or symptoms of the disease or prevent progression thereof; as would be understood in the medical arts, cure, although desired, is not required.

The therapeutically effective dose of the pharmaceutical agents of the present invention can be estimated initially by *in vitro* tests, such as cell culture assays, followed by assay in model animals, usually mice, rats, rabbits, dogs, or pigs. The animal model can also be used to determine an initial preferred concentration range and route of administration.

For example, the ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population) can be determined in one or more cell culture or animal model systems. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as LD50/ED50. Pharmaceutical compositions that exhibit large therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies are used in formulating an initial dosage range for human use, and preferably provide a range of circulating concentrations that includes the ED50 with little or no toxicity. After administration, or between successive administrations, the circulating concentration of active agent varies within this range depending upon pharmacokinetic factors well known in the art, such as the dosage form employed, sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors specific to the subject requiring treatment. Factors that can be taken into account by the practitioner include the severity of the disease state, general health of the subject, age, weight, gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. Where the therapeutic agent is a protein or antibody of the present invention, the therapeutic protein or antibody agent typically is administered at a daily dosage of 0.01 mg to 30 mg/kg of body weight of 5 the patient (e.g., 1mg/kg to 5 mg/kg). The pharmaceutical formulation can be administered in multiple doses per day, if desired, to achieve the total desired daily dose.

- Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors.
- 10 Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical formulation(s) of the present invention to the patient. The pharmaceutical compositions of the present invention can be administered 15 alone, or in combination with other therapeutic agents or interventions.

#### Therapeutic Methods

The present invention further provides methods of treating subjects having defects in a gene of the invention, e.g., in expression, activity, distribution, localization, and/or solubility, which can manifest as a disorder of breast function. As used herein, "treating" 20 includes all medically-acceptable types of therapeutic intervention, including palliation and prophylaxis (prevention) of disease. The term "treating" encompasses any improvement of a disease, including minor improvements. These methods are discussed below.

##### *Gene Therapy and Vaccines*

25 The isolated nucleic acids of the present invention can also be used to drive *in vivo* expression of the polypeptides of the present invention. *In vivo* expression can be driven from a vector, typically a viral vector, often a vector based upon a replication incompetent retrovirus, an adenovirus, or an adeno-associated virus (AAV), for the purpose of gene therapy. *In vivo* expression can also be driven from signals endogenous to the nucleic acid 30 or from a vector, often a plasmid vector, such as pVAX1 (Invitrogen, Carlsbad, CA, USA), for purpose of "naked" nucleic acid vaccination, as further described in U.S. Patent Nos. 5,589,466; 5,679,647; 5,804,566; 5,830,877; 5,843,913; 5,880,104; 5,958,891;

5,985,847; 6,017,897; 6,110,898; 6,204,250, the disclosures of which are incorporated herein by reference in their entireties. For cancer therapy, it is preferred that the vector also be tumor-selective. *See, e.g.*, Doronin *et al.*, *J. Virol.* 75: 3314-24 (2001).

In another embodiment of the therapeutic methods of the present invention, a  
5 therapeutically effective amount of a pharmaceutical composition comprising a nucleic acid molecule of the present invention is administered. The nucleic acid molecule can be delivered in a vector that drives expression of a BSP, fusion protein, or fragment thereof, or without such vector. Nucleic acid compositions that can drive expression of a BSP are administered, for example, to complement a deficiency in the native BSP, or as DNA  
10 vaccines. Expression vectors derived from virus, replication deficient retroviruses, adenovirus, adeno-associated (AAV) virus, herpes virus, or vaccinia virus can be used as can plasmids. *See, e.g.*, Cid-Arregui, *supra*. In a preferred embodiment, the nucleic acid molecule encodes a BSP having the amino acid sequence of SEQ ID NO: 95-156, or a fragment, fusion protein, allelic variant or homolog thereof.

15 In still other therapeutic methods of the present invention, pharmaceutical compositions comprising host cells that express a BSP, fusions, or fragments thereof can be administered. In such cases, the cells are typically autologous, so as to circumvent xenogeneic or allotypic rejection, and are administered to complement defects in BSP production or activity. In a preferred embodiment, the nucleic acid molecules in the cells  
20 encode a BSP having the amino acid sequence of SEQ ID NO: 95-156, or a fragment, fusion protein, allelic variant or homolog thereof.

#### *Antisense Administration*

Antisense nucleic acid compositions, or vectors that drive expression of a BSG  
25 antisense nucleic acid, are administered to downregulate transcription and/or translation of a BSG in circumstances in which excessive production, or production of aberrant protein, is the pathophysiologic basis of disease.

Antisense compositions useful in therapy can have a sequence that is complementary to coding or to noncoding regions of a BSG. For example, oligonucleotides derived from the transcription initiation site, *e.g.*, between positions -10  
30 and +10 from the start site, are preferred.

Catalytic antisense compositions, such as ribozymes, that are capable of sequence-specific hybridization to BSG transcripts, are also useful in therapy. *See, e.g.*,

Phylactou, *Adv. Drug Deliv. Rev.* 44(2-3): 97-108 (2000); Phylactou *et al.*, *Hum. Mol. Genet.* 7(10): 1649-53 (1998); Rossi, *Ciba Found. Symp.* 209: 195-204 (1997); and Sigurdsson *et al.*, *Trends Biotechnol.* 13(8): 286-9 (1995).

Other nucleic acids useful in the therapeutic methods of the present invention are those that are capable of triplex helix formation in or near the BSG genomic locus. Such triplexing oligonucleotides are able to inhibit transcription. See, e.g., Intody *et al.*, *Nucleic Acids Res.* 28(21): 4283-90 (2000); and McGuffie *et al.*, *Cancer Res.* 60(14): 3790-9 (2000). Pharmaceutical compositions comprising such triplex forming oligos (TFOs) are administered in circumstances in which excessive production, or production of aberrant protein, is a pathophysiologic basis of disease.

In a preferred embodiment, the antisense molecule is derived from a nucleic acid molecule encoding a BSP, preferably a BSP comprising an amino acid sequence of SEQ ID NO: 95-156, or a fragment, allelic variant or homolog thereof. In a more preferred embodiment, the antisense molecule is derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-94, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

#### *Polypeptide Administration*

In one embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a BSP, a fusion protein, fragment, analog or derivative thereof is administered to a subject with a clinically-significant BSP defect.

Protein compositions are administered, for example, to complement a deficiency in native BSP. In other embodiments, protein compositions are administered as a vaccine to elicit a humoral and/or cellular immune response to BSP. The immune response can be used to modulate activity of BSP or, depending on the immunogen, to immunize against aberrant or aberrantly expressed forms, such as mutant or inappropriately expressed isoforms. In yet other embodiments, protein fusions having a toxic moiety are administered to ablate cells that aberrantly accumulate BSP.

In a preferred embodiment, the polypeptide administered is a BSP comprising an amino acid sequence of SEQ ID NO: 95-156, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the polypeptide is encoded

by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-94, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

*Antibody, Agonist and Antagonist Administration*

In another embodiment of the therapeutic methods of the present invention, a  
5 therapeutically effective amount of a pharmaceutical composition comprising an antibody  
(including fragment or derivative thereof) of the present invention is administered. As is  
well known, antibody compositions are administered, for example, to antagonize activity  
of BSP, or to target therapeutic agents to sites of BSP presence and/or accumulation. In a  
10 preferred embodiment, the antibody specifically binds to a BSP comprising an amino acid  
sequence of SEQ ID NO: 95-156, or a fusion protein, allelic variant, homolog, analog or  
derivative thereof. In a more preferred embodiment, the antibody specifically binds to a  
BSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-  
15 94, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

The present invention also provides methods for identifying modulators which  
15 bind to a BSP or have a modulatory effect on the expression or activity of a BSP.  
Modulators which decrease the expression or activity of BSP (antagonists) are believed to  
be useful in treating breast cancer. Such screening assays are known to those of skill in  
the art and include, without limitation, cell-based assays and cell-free assays. Small  
molecules predicted via computer imaging to specifically bind to regions of a BSP can  
20 also be designed, synthesized and tested for use in the imaging and treatment of breast  
cancer. Further, libraries of molecules can be screened for potential anticancer agents by  
assessing the ability of the molecule to bind to the BSPs identified herein. Molecules  
identified in the library as being capable of binding to a BSP are key candidates for further  
evaluation for use in the treatment of breast cancer. In a preferred embodiment, these  
25 molecules will downregulate expression and/or activity of a BSP in cells.

In another embodiment of the therapeutic methods of the present invention, a  
pharmaceutical composition comprising a non-antibody antagonist of BSP is administered.  
Antagonists of BSP can be produced using methods generally known in the art. In  
particular, purified BSP can be used to screen libraries of pharmaceutical agents, often  
30 combinatorial libraries of small molecules, to identify those that specifically bind and  
antagonize at least one activity of a BSP.

In other embodiments a pharmaceutical composition comprising an agonist of a BSP is administered. Agonists can be identified using methods analogous to those used to identify antagonists.

In a preferred embodiment, the antagonist or agonist specifically binds to and  
5 antagonizes or agonizes, respectively, a BSP comprising an amino acid sequence of SEQ ID NO: 95-156, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the antagonist or agonist specifically binds to and  
antagonizes or agonizes, respectively, a BSP encoded by a nucleic acid molecule having a  
nucleotide sequence of SEQ ID NO: 1-94, or a part, allelic variant, substantially similar or  
10 hybridizing nucleic acid thereof.

#### *Targeting breast Tissue*

The invention also provides a method in which a polypeptide of the invention, or  
an antibody thereto, is linked to a therapeutic agent such that it can be delivered to the  
15 breast or to specific cells in the breast. In a preferred embodiment, an anti-BSP antibody  
is linked to a therapeutic agent and is administered to a patient in need of such therapeutic  
agent. The therapeutic agent may be a toxin, if breast tissue needs to be selectively  
destroyed. This would be useful for targeting and killing breast cancer cells. In another  
embodiment, the therapeutic agent may be a growth or differentiation factor, which would  
20 be useful for promoting breast cell function.

In another embodiment, an anti-BSP antibody may be linked to an imaging agent  
that can be detected using, e.g., magnetic resonance imaging, CT or PET. This would be  
useful for determining and monitoring breast function, identifying breast cancer tumors,  
and identifying noncancerous breast diseases.

25

## EXAMPLES

### **Example 1: Gene Expression analysis**

Identification of BSGs was carried out by a systematic analysis of gene expression data in the LIFESEQ® Gold database available from Incyte Genomics Inc, Palo Alto, CA, using the data mining software package CLASP™.

30

The CLASP target gene identification process is focused on, but not limited to, the following 4 CLASP profiles: tissue specific expression, cancer specific expression, differentially expressed in cancer, maximum tissue differential expression.

- (1) For these profiles:cDNA libraries were divided into 48 unique tissue organs. The genes were grouped into gene bins, each bin is a sequence based cluster grouped together with a common contig. The expression levels for each gene bin were calculated in each organ. Differential expression significance was calculated with rigorous statistical significant test considering the influence of sequence random fluctuations and sampling size of cDNA libraries from concept published by Audic S and Claverie JM (Genome Res 1997 7(10): 986-995: The significance of digital gene expression profiles).
- (2) Highly expressed organ specific genes were selected based on the percentage abundance level in the targeted organ versus all the other organs (organ-specificity).
- (3) The expression levels of each highly expressed organ-specific gene in the tumor tissue libraries were compared with normal tissue libraries and tissue libraries associated with tumor or disease (cancer-specificity) and analyzed for statistical significance.
- (4) Target genes exhibiting each CLASP profile criteria were selected
- CLASP tissue specific expression profile: In order to meet the organ-specificity criteria, the expression level of the component clones which the gene is composed of must exhibit 3 or more occurrences regardless the total number of genes isolated for the target organ. The percentage abundance level in each organ was calculated to identify the organ with the highest expression percentage level.
- CLASP cancer specific expression profile: In order to fulfill the cancer specific criteria, genes must exhibit 0 expression in normal and libraries associated with tumor and disease but not tumor per se. If the gene then exhibited organ-specificity, the gene was selected as a CLASP target for this profile.
- CLASP differentially expressed in cancer profile: Expression levels in tumor libraries in each organ and normal libraries (including normal libraries associated with cancer or disease) for all organs were obtained and statistically analyzed. If the gene exhibited 90% of confidence that it is over-expressed in tumor libraries in the target organ than normal libraries for all organs, it was selected as a CLASP target for this profile.

- CLASP maximum tissue differential expression profile: CLASP targets were selected based on ratio of expression in tumor libraries compared to expression in normal libraries (including normal libraries associated with tumor or disease) for each organ regardless of whether the gene exhibited organ-specificity. This profile was divided into 2 sub-profiles, since the ratio of expression cannot be obtained if no expression is present in normal libraries (including normal libraries associated with tumor or disease). In this case, the maximum expression percentage of the gene, as calculated by the occurrence of the gene divided by the occurrence of all genes in the target organ, was used. CLASP selects the top 50 targets for each sub-profile.
- Accordingly, CLASP allows the identification of highly expressed organ and cancer specific genes based on the gene expression levels in each tissue organ. CLASP scores for a portion of the BSG of this invention are listed below.

DEX0321_1	SEQ ID NO: 1	CLASP5 CLASP3
DEX0321_4	SEQ ID NO: 4	CLASP5 CLASP1
DEX0321_5	SEQ ID NO: 5	CLASP5
DEX0321_6	SEQ ID NO: 6	CLASP5
DEX0321_7	SEQ ID NO: 7	CLASP5 CLASP3
DEX0321_10	SEQ ID NO: 10	CLASP5
DEX0321_11	SEQ ID NO: 11	CLASP5
DEX0321_12	SEQ ID NO: 12	CLASP5 CLASP4
DEX0321_13	SEQ ID NO: 13	CLASP5 CLASP4
DEX0321_14	SEQ ID NO: 14	CLASP5 CLASP3 CLASP4
DEX0321_15	SEQ ID NO: 15	CLASP5 CLASP4
DEX0321_16	SEQ ID NO: 16	CLASP5 CLASP4
DEX0321_17	SEQ ID NO: 17	CLASP5 CLASP4
DEX0321_18	SEQ ID NO: 18	CLASP5 CLASP4
DEX0321_21	SEQ ID NO: 21	CLASP5
DEX0321_22	SEQ ID NO: 22	CLASP5
DEX0321_23	SEQ ID NO: 23	CLASP5
DEX0321_24	SEQ ID NO: 24	CLASP5
DEX0321_25	SEQ ID NO: 25	CLASP5
DEX0321_26	SEQ ID NO: 26	CLASP5 CLASP3
DEX0321_27	SEQ ID NO: 27	CLASP5 CLASP4
DEX0321_28	SEQ ID NO: 28	CLASP5
DEX0321_29	SEQ ID NO: 29	CLASP5
DEX0321_30	SEQ ID NO: 30	CLASP5 CLASP4
DEX0321_31	SEQ ID NO: 31	CLASP5
DEX0321_32	SEQ ID NO: 32	CLASP5
DEX0321_33	SEQ ID NO: 33	CLASP5 CLASP4
DEX0321_34	SEQ ID NO: 34	CLASP5 CLASP4
DEX0321_35	SEQ ID NO: 35	CLASP5
DEX0321_36	SEQ ID NO: 36	CLASP5
DEX0321_37	SEQ ID NO: 37	CLASP5
DEX0321_38	SEQ ID NO: 38	CLASP5 CLASP4 CLASP3
DEX0321_41	SEQ ID NO: 41	CLASP5
DEX0321_42	SEQ ID NO: 42	CLASP5
DEX0321_43	SEQ ID NO: 43	CLASP5 CLASP4 CLASP3
DEX0321_44	SEQ ID NO: 44	CLASP5

DEX0321_45	SEQ ID NO: 45	CLASP2 CLASP1
DEX0321_46	SEQ ID NO: 46	CLASP2 CLASP1
DEX0321_47	SEQ ID NO: 47	CLASP5 CLASP4 CLASP3

In addition the expression values for each organ in the format 9 - 0.9999 are listed. Each box first lists the given organ, then it lists a number representing the percentage of the expression of the gene in the given organ.

321_1	MAM .0085	BRN .0002	ADR .0015	BLV .0016	UTR .0019
321_4	MAM .0028	BRN .0001	FTS .0001	BRN .0002	INL .0004
321_5	MAM .0009				
321_6	MAM .0009				
321_7	MAM .0383	UNC .004	TNS .0054	PIT .0123	PLE .015
321_10		OVR .0051	FAL .0063		
321_11		OVR .0051	FAL .0063		
321_12	MAM .0047	PRO .0006	INL .0006	UTR .0013	ADR .0015
321_13	MAM .0047	PRO .0006	INL .0006	UTR .0013	ADR .0015
321_14	MAM .0727	BLO .008	BLO .008	UNC .008	UNC .008
321_15	MAM .2073	FAL .0126	PIB .0181	PLE .0299	SPC .035
321_16	MAM .2073	FAL .0126	PIB .0181	PLE .0299	SPC .035
321_17	MAM .529	BMR .1609	SAG .1778	SPC .1899	NOS .198
321_18	MAM .529	BMR .1609	SAG .1778	SPC .1899	NOS .198
321_21	MAM .0005				
321_22	MAM .0005				
321_23	MAM .0005				.
321_24	MAM .0005				
321_25		PAN .027	BRN .0319	LIV .0435	ADR .0522
321_26	MAM .0453	ESO .0051	BON .0112	INS .0124	CRD .0136
321_27	MAM .1181	NOS .0147	URE .0225	LIV .0246	BON .0394
321_28	MAM .0005				
321_29	MAM .0009	OVR .001			
321_30	MAM .0052	CON .0023	PNS .0023	PAN .0024	ADR .003

321_31	MAM .0142	PRO .013	ADR .0149	LNG .0156	
321_32	MAM .0142	PRO .013	ADR .0149	LNG .0156	
321_33	MAM .0057	FTS .0006	OVR .001	BLD .0016	TST .0027
321_34	MAM .0057	FTS .0006	OVR .001	BLD .0016	TST .0027
321_35	MAM .0213	OVR .0226	BLD .0241	INL .0275	LNG .0374
321_36	MAM .0213	OVR .0226	BLD .0241	INL .0275	LNG .0374
321_37	MAM .0123	PNS .0023	INL .0032	PRO .0034	BON .0056
321_38	MAM .0151	KID .0013	KID .0013	FTS .0015	FTS .0015
321_41	MAM .0024	LIV .0019			
321_42	MAM .0024	LIV .0019			
321_43	MAM .042	SEB .0104	SEB .0104	BON .0169	BON .0169
321_44	MAM .0005				
321_45	MAM .0053	LNG .0003	LMN .0034	TNS .0049	LMN .0099
321_46	MAM .0053	LNG .0003	LMN .0034	TNS .0049	LMN .0099
321_47	MAM .8365	PLE .0449	PLE .0449	SPC .085	SPC .085

## Abbreviation for tissues:

- ADR Adrenal Glands  
 BLD Bladder  
 BLO Blood  
 5 BLV Blood Vessels  
 BMR Bone Marrow  
 BON Bones  
 BRN Brain  
 CON Connective Tissue  
 10 CRD Heart  
 ESO Esophagus  
 FAL Fallopian Tubes  
 FTS Fetus  
 INL Intestine, Large  
 15 INS Intestine, Small  
 KID Kidney  
 LIV Liver  
 LMN Lymphoid Tissue  
 LNG Lung  
 20 MAM Breast  
 NOS Nose  
 OVR Ovary  
 PAN Pancreas  
 PIB Pineal Body  
 25 PIT Pituitary Gland  
 PLE Pleura  
 PNS Penis  
 PRO Prostate  
 SAG Salivary Glands  
 30 SEB Seminal Vesicles  
 SPC Spinal Cord  
 TNS Tonsil / Adenoids  
 TST Testis  
 UNC Mixed Tissues  
 35 URE Ureter  
 UTR Uterus

Based on sequence alignment with the human genome, the following chromosomal locations were assigned. The mapping of the nucleic acid ("NT") SEQ ID NO; NT DEX ID; Parent NT DEX ID; chromosomal location (if known); open reading frame (ORF) 5 location; amino acid ("AA") SEQ ID NO; AA DEX ID; and Parent AA DEX ID are shown in the table below

SEQ ID NO	DEX NT SEQ ID	PARENT DEX NT	Microarray IN	Chromo Map	ORF Loc	SEQ ID NO	DEX AA SEQ ID	PARENT DEX AA
1 DEX0432_001.nt.1	DEX0321_1	mry4259	8					
2 DEX0432_002.nt.1	DEX0321_2	mry4507	6					
3 DEX0432_003.nt.1	DEX0321_3	mry4560	11					
4 DEX0432_004.nt.1	DEX0321_4	mry4787	3					
5 DEX0432_005.nt.1	DEX0321_5	mry4902			95	DEX0432_005.aa.1	DEX0321_48	
6 DEX0432_006.nt.1	DEX0321_6	flex						
7 DEX0432_007.nt.1	DEX0321_7	mry4934	12					
8 DEX0432_008.nt.1	DEX0321_8	mry5572	5					
9 DEX0432_009.nt.1	DEX0321_9	mry5640	5					
10 DEX0432_010.nt.1	DEX0321_10	mry5685	1		96	DEX0432_010.aa.1	DEX0321_49	
11 DEX0432_011.nt.1	DEX0321_11	flex	1					
12 DEX0432_012.nt.1	DEX0321_12	mry5824	1		97	DEX0432_012.aa.1	DEX0321_50	
13 DEX0432_013.nt.1	DEX0321_13	flex	1		98	DEX0432_013.aa.1	DEX0321_51	
14 DEX0432_014.nt.1	DEX0321_14	mry5904	2					
15 DEX0432_015.nt.1	DEX0321_15	mry5988	15		99	DEX0432_015.aa.1	DEX0321_52	
16 DEX0432_016.nt.1	DEX0321_16	flex	15		100	DEX0432_016.aa.1	DEX0321_53	
17 DEX0432_017.nt.1	DEX0321_17	mry6191	X		101	DEX0432_017.aa.1	DEX0321_54	
18 DEX0432_018.nt.1	DEX0321_18	flex	6		102	DEX0432_018.aa.1	DEX0321_55	
19 DEX0432_019.nt.1	DEX0321_19	mry6723	5		103	DEX0432_019.aa.1	DEX0321_56	
20 DEX0432_020.nt.1	DEX0321_20	flex	5					
21 DEX0432_021.nt.1	DEX0321_21	mry6804	2		104	DEX0432_021.aa.1	DEX0321_57	
22 DEX0432_022.nt.1	DEX0321_22	flex	2					
23 DEX0432_023.nt.1	DEX0321_23	mry6804						
24 DEX0432_024.nt.1	DEX0321_24	flex	8		105	DEX0432_023.aa.1	DEX0321_58	
		mry7407						

- 122 -

25	DEX0432_025.nt.1	DEX0321_25	mry7505	20		106	DEX0432_025.aa.1	DEX0321_59
26	DEX0432_026.nt.1	DEX0321_26	flex	20		107	DEX0432_026.aa.1	DEX0321_60
27	DEX0432_027.nt.1	DEX0321_27	mry7575	19				
28	DEX0432_028.nt.1	DEX0321_28	mry7689	18				
29	DEX0432_029.nt.1	DEX0321_29	mry7812	2				
30	DEX0432_030.nt.1	DEX0321_30	mry7951	8		108	DEX0432_031.aa.1	DEX0321_61
31	DEX0432_031.nt.1	DEX0321_31	mry8181	7				
32	DEX0432_032.nt.1	DEX0321_32	flex	7				
33	DEX0432_033.nt.1	DEX0321_33	mry8214	18		109	DEX0432_033.aa.1	DEX0321_62
34	DEX0432_034.nt.1	DEX0321_34	flex	18				
35	DEX0432_035.nt.1	DEX0321_35	mry8268	1		110	DEX0432_035.aa.1	DEX0321_63
36	DEX0432_036.nt.1	DEX0321_36	flex	1				
37	DEX0432_036.nt.2		*	73-	111	DEX0432_036.aa.2		
38	DEX0432_036.nt.3		*	73-	112	DEX0432_036.aa.3		
39	DEX0432_036.nt.4		*	73-	113	DEX0432_036.aa.4		
40	DEX0432_036.nt.5		*	1648				
41	DEX0432_036.nt.6		*	73-	114	DEX0432_036.aa.5		
42	DEX0432_036.nt.7		*	1621				
43	DEX0432_036.nt.8		1q22	184-	117	DEX0432_036.aa.8		
44	DEX0432_036.nt.9		1q22	184-	117	DEX0432_036.aa.8		
45	DEX0432_036.nt.10		1q22	1612				
46	DEX0432_036.nt.11		1q22	836-	118	DEX0432_036.aa.10		
47	DEX0432_036.nt.12		1q22	1530				
				195-	119	DEX0432_036.aa.11		
				519				
				184-	120	DEX0432_036.aa.12		
				1639				

- 123 -

48	DEX0432_036.nt.13		1q22	184- 1576	121	DEX0432_036.aa.13
49	DEX0432_036.nt.14		1q22	49- 1625	122	DEX0432_036.aa.14
50	DEX0432_036.nt.15		1q22	184- 1492	123	DEX0432_036.aa.15
51	DEX0432_036.nt.16		1q22	184- 1006	124	DEX0432_036.aa.16
52	DEX0432_036.nt.17		1q22	184- 1237	125	DEX0432_036.aa.17
53	DEX0432_036.nt.18		1q22	184- 1639	120	DEX0432_036.aa.12
54	DEX0432_036.nt.19		1q22	184- 1135	126	DEX0432_036.aa.19
55	DEX0432_036.nt.20		1q22	184- 877	127	DEX0432_036.aa.20
56	DEX0432_036.nt.21		1q22	184- 2029	128	DEX0432_036.aa.21
57	DEX0432_036.nt.22		1q22	184- 1303	129	DEX0432_036.aa.22
58	DEX0432_036.nt.23		1q22	184- 955	130	DEX0432_036.aa.23
59	DEX0432_036.nt.24		1q22	184- 1663	131	DEX0432_036.aa.24
60	DEX0432_036.nt.25		1q22	184- 1634	132	DEX0432_036.aa.25
61	DEX0432_036.nt.26		1q22	184- 637	133	DEX0432_036.aa.26
62	DEX0432_036.nt.27		1q22	184- 691	134	DEX0432_036.aa.27
63	DEX0432_036.nt.28		1q22	1- 242	135	DEX0432_036.aa.28
64	DEX0432_036.nt.29		1q22	184- 1378	136	DEX0432_036.aa.29
65	DEX0432_036.nt.30		1q22	1- 113	137	DEX0432_036.aa.30

66	DEX0432_036.nt.31			1q22	184-	138	DEX0432_036.aa.31
67	DEX0432_036.nt.32			1q22	184-	139	DEX0432_036.aa.32
68	DEX0432_036.nt.33			1q22	34-	140	DEX0432_036.aa.33
69	DEX0432_036.nt.34			1q22	380-	141	DEX0432_036.aa.34
70	DEX0432_036.nt.35			1q22	39-	142	DEX0432_036.aa.35
71	DEX0432_036.nt.36			1q22	184-	143	DEX0432_036.aa.36
72	DEX0432_036.nt.37			1q22	184-	144	DEX0432_036.aa.37
73	DEX0432_036.nt.38			1q22	417-	145	DEX0432_036.aa.38
74	DEX0432_036.nt.39			1q22	184-	146	DEX0432_036.aa.39
75	DEX0432_036.nt.40			1q22	184-	139	DEX0432_036.aa.32
76	DEX0432_036.nt.41			1q22	184-	147	DEX0432_036.aa.41
77	DEX0432_036.nt.42			1q22	184-	148	DEX0432_036.aa.42
78	DEX0432_036.nt.43			1q22	184-	149	DEX0432_036.aa.43
79	DEX0432_036.nt.44			1q22	184-	150	DEX0432_036.aa.44
80	DEX0432_036.nt.45			1q22	1-	151	DEX0432_036.aa.45
81	DEX0432_036.nt.46			1q22	334		
82	DEX0432_036.nt.47			1q22	184-	152	DEX0432_036.aa.46
83	DEX0432_036.nt.48			1q22	568		
84	DEX0432_037.nt.1	DEX0321_37	mry8376	17	-	153	DEX0432_036.aa.48
85	DEX0432_038.nt.1	DEX0321_38	mry8420	1			

86	DEX0432_039.nt.1	DEX0321_39	mry8476	9		154	DEX0432_039.aa.1	DEX0321_64
87	DEX0432_040.nt.1	DEX0321_40	flex mry8476	9				
88	DEX0432_041.nt.1	DEX0321_41	mry8502	17		155	DEX0432_041.aa.1	DEX0321_65
89	DEX0432_042.nt.1	DEX0321_42	flex mry8502	17				
90	DEX0432_043.nt.1	DEX0321_43	mry8644	1				
91	DEX0432_044.nt.1	DEX0321_44	mry8764	18				
92	DEX0432_045.nt.1	DEX0321_45	mry8936	4		156	DEX0432_045.aa.1	DEX0321_66
93	DEX0432_046.nt.1	DEX0321_46	flex mry8936	4				
94	DEX0432_047.nt.1	DEX0321_47	mry9072	2				

The microarray sequence identifications, extended sequences based human genome (flex) and predicted peptide sequences for each of the targets are listed below:

	SEQ ID NO	Microarray IN	Predicted Peptide
5	DEX0321_1	mry4259	
	DEX0321_2	mry4507	
	DEX0321_3	mry4560	
	DEX0321_4	mry4787	
10	DEX0321_5	mry4902	DEX0321_48
	DEX0321_6	flex mry4902	
	DEX0321_7	mry5434	
	DEX0321_8	mry5572	
	DEX0321_9	mry5640	
15	DEX0321_10	mry5685	DEX0321_49
	DEX0321_11	flex mry5685	
	DEX0321_12	mry5824	DEX0321_50
	DEX0321_13	flex mry5824	DEX0321_51
	DEX0321_14	mry5904	
20	DEX0321_15	mry5988	DEX0321_52
	DEX0321_16	flex mry5988	DEX0321_53
	DEX0321_17	mry6191	DEX0321_54
	DEX0321_18	flex mry6191	DEX0321_55
	DEX0321_19	mry6723	DEX0321_56
25	DEX0321_20	flex mry6723	
	DEX0321_21	mry6804	DEX0321_57
	DEX0321_22	flex mry6804	
	DEX0321_23	mry7407	DEX0321_58
	DEX0321_24	flex mry7407	
30	DEX0321_25	mry7505	DEX0321_59
	DEX0321_26	flex mry7505	DEX0321_60
	DEX0321_27	mry7575	
	DEX0321_28	mry7689	
	DEX0321_29	mry7812	
35	DEX0321_30	mry7951	
	DEX0321_31	mry8181	DEX0321_61
	DEX0321_32	flex mry8181	
	DEX0321_33	mry8214	DEX0321_62
	DEX0321_34	flex mry8214	
40	DEX0321_35	mry8268	DEX0321_63
	DEX0321_36	flex mry8268	
	DEX0321_37	mry8376	
	DEX0321_38	mry8420	
	DEX0321_39	mry8476	DEX0321_64
45	DEX0321_40	flex mry8476	
	DEX0321_41	mry8502	DEX0321_65
	DEX0321_42	flex mry8502	
	DEX0321_43	mry8644	
	DEX0321_44	mry8764	
50	DEX0321_45	mry8936	DEX0321_66
	DEX0321_46	flex mry8936	
	DEX0321_47	mry9072	

**Example 1A: Suppression subtractive hybridization (Clontech PCR-SELECT)**

55 Clontech PCR-SELECT is a PCR based subtractive hybridization method designed to selectively enrich for cDNAs corresponding to mRNAs differentially expressed between two mRNA populations (Diatchenko et al, Proc. Natl. Acad. Sci. USA, Vol. 93,

pp. 6025-6030, 1996). Clontech PCR-SELECT is a method for enrichment of differentially expressed mRNAs based on a selective amplification. cDNA is prepared from the two mRNA populations which are to be compared (Tester: cDNA population in which the differentially expressed messages are sought and Driver: cDNA population in which the differentially expressed transcripts are absent or low). The tester sample is separated in two parts and different PCR adapters are ligated to the 5' ends. Each tester is separately annealed to excess driver (first annealing) and then pooled and again annealed (second annealing) to excess driver. During the first annealing sequences common to both populations anneal. Additionally the concentration of high and low abundance messages are normalized since annealing is faster for abundant molecules due to the second order kinetics of hybridization. During the second annealing cDNAs unique or overabundant to the tester can anneal together. Such molecules have different adapters at their ends. The addition of additional driver during the second annealing enhances the enrichment of the desired differentially expressed sequences. During subsequent PCR, molecules that have different adapters at each end amplify exponentially. Molecules which have identical adapters, or adapters at only one end, or no adapters (driver sequences) either do not amplify or undergo linear amplification. The end result is enrichment for cDNAs corresponding to differentially expressed messages (unique to the tester or upregulated in the tester). This technique was used to identify transcripts unique to breast tissue or messages overexpressed in breast cancer. Pairs of matched samples isolated from the same patient, a cancer sample, and the "normal" adjacent tissue from the same tissue type were utilized. The mRNA from the cancer tissue is used as the "tester", and the non-cancer mRNA as a "driver". The non-cancer "driver" is from the same individual and tissue as the cancer sample (Matched). Alternatively, the "driver" can be from a different individual but the same tissue as the tumor sample (unmatched). In some cases mixtures of mRNAs derived from non-cancer tissues types different from the cancer tissue type are also used as "drivers". The last approach allows the identification of transcripts whose expression is specific or upregulated in the cancer tissue type analyzed. Such transcripts may or may not be cancer specific in their expression.

Several subtracted libraries were generated for breast tissue. The product of the subtraction experiments was used to generate cDNA libraries. These cDNA libraries contain Expressed Sequence Tags (ESTs) from genes that are breast cancer specific, or upregulated in breast tissue. Randomized clones picked from each cDNA PCR Select

library were sequenced and the genes identified by a systematic analysis of the sequence data against the LIFESEQ Gold database available from Incyte Pharmaceuticals, Palo Alto. All of the lead sequences were discovered using subtractions.

#### **Example 1b: Alternative Splice Variants**

5 We identified gene transcripts associated with cancer disease, development, or progression using cloning experiments, the Gencarta™ tools software (CompuGen Ltd., Tel Aviv, Israel), and a variety of public and proprietary databases. These transcripts are either novel splice variant sequences which differ from a previously defined sequence or new uses of known sequences. In general the previously defined sequence for a transcript  
10 family is annotated as DEX0432\_XXX.nt.1 and the novel variants are annotated as DEX0432\_XXX.nt.2, DEX0432\_XXX.nt.3, etc. The novel variant DNA sequences encode novel proteins which differ from a previously defined protein sequence. In relation to the nucleotide sequence naming convention, the previously defined amino acid sequence is annotated DEX0432\_XXX.aa.1 and the novel variants annotated as  
15 DEX0432\_XXX.aa.2, etc.

#### *EST Support*

The alternative splice variants are predicted by computational analysis of Expressed Sequence Tags (ESTs) derived from public and proprietary cDNA libraries and genomic information. A novel transcript may be supported by numerous ESTs.

20 *SAGE Support*

Serial Analysis of Gene Expression (SAGE) tag data analysis is performed on the novel splice variants. Gencarta™ tools (CompuGen Ltd., Tel Aviv, Israel) report SAGE tag data for individual transcripts when available. SAGE data includes the SAGE tag sequence for the novel transcripts, expression level (as a ratio) of the SAGE tag in tissue  
25 samples, the source or tissue, state or disease condition of the tissue, tissue sample type, and a description of the tissue samples. SAGE tag data analysis results are disclosed and discussed in each transcript section below.

#### *Sequence Alignment Support*

Alignments of previously identified and novel splice variant sequences are  
30 performed to confirm unique portions of splice variant nucleic acid and amino acid sequences. The alignments are done using the Needle program in the European Molecular

Biology Open Software Suite (EMBOSS) version 2.2.0 available at [www.emboss.org](http://www.emboss.org) from EMBnet (<http://www.embnet.org>). Default settings are used unless otherwise noted. The Needle program in EMBOSS implements the Needleman-Wunsch algorithm. Needleman, S. B., Wunsch, C. D., *J. Mol. Biol.* 48:443-453 (1970).

5 It is well known to those skilled in the art that implication of alignment algorithms by various programs may result in minor changes in the generated output. These changes include but are not limited to: alignment scores (percent identity, similarity, and gap), display of nonaligned flanking sequence regions, and number assignment to residues. These minor changes in the output of an alignment do not alter the physical characteristics  
10 of the sequences or the differences between the sequences, e.g. regions of homology, insertions, or deletions. Descriptions of alignments are provided in each splice variant family section.

DEX0432\_035.nt.1, DEX0432\_036.nt.1 (Mam096); Splice Variants DEX0432\_036.nt.2 – DEX0432\_036.nt.48 (Mam096v)

15 Novel transcripts of the Mam096 family which include variants DEX0432\_35.nt.1 and DEX0432\_36.nt.1 – DEX0432\_36.nt.48, were discovered using the methods described above. The use of "Mam096" herein refers to the transcript family and is meant to include the variants known in the literature. Mam096 has also been identified as Glycoprotein 39 3' fragment in JP 07051065-A; Human cancer associated gene sequence  
20 SEQ ID NO:19 in WO 005/5350-A1; Thyroid cancer related gene sequence SEQ ID NO:5876 in WO 01/94629-A2; and Human gene expression profile polynucleotide SEQ ID NO 339 in WO 02/74979-A2 which are herein incorporated by reference.

In addition to the nomenclature from the patents above, there are many synonyms for Mam096 in the literature. They include Mucin 1 precursor (MUC-1), Polymorphic epithelial mucin (PEM) (PEMT), Episialin, Tumor-associated mucin, Carcinoma-associated mucin, Tumor-associated epithelial membrane antigen (EMA), H23AG, Peanut-reactive urinary mucin (PUM), Breast carcinoma-associated antigen DF3, and CD227 antigen. Lan,M.S., *et al.* (1990) *J. Biol. Chem.* 265:15294-15299; Ligtenberg,M.J.L., *et al.* (1990) *J. Biol. Chem.* 265:5573-5578; Gandler,S.J., *et al.* (1990)  
25 *J. Biol. Chem.* 265:15286-15293; Lancaster,C.A., *et al.* (1990) *Biochem. Biophys. Res. Commun.* 173:1019-1029; Wreschner,D.H., *et al.* (1990) *Eur. J. Biochem.* 189:463-473;  
30 Hareveni,M., *et al.* (1990) *Eur. J. Biochem.* 189:475-486; Tsarfaty,I. *Et al.*( 1990) *Gene*

93:313-318; Zrihan-Licht,S., *et al.* (1994) *Eur. J. Biochem.* 224:787-795;  
Oosterkamp,H.M. *et al.* (1997) *Int. J. Cancer* 72:87-94; Zhang,L.X. *et al.* Molecular  
cloning of an isoform of MUC1, MUC1/Y. Submitted FEB-1999 to the EMBL GenBank  
DDBJ databases (Isoform 7); Zhang,L.X. *et al.* Cloning of a new potential secreted short  
5 variant form of MUC1 mucin in epithelial cancer cell line. Submitted FEB-2001 to the  
EMBL GenBank DDBJ databases (Isoform 9); Gendler,S.J. *et al.* (1988) *J. Biol. Chem.*  
263:12820-12823; Abe,M. *et al.* (1989) *Biochem. Biophys. Res. Commun.* 165:644-649;  
Weiss,M. *et al.* (1996) *Int. J. Cancer* 66:55-59; Yu,C.J. *et al.* (1996) *Oncology* 53:118-  
126; Buluwela,L. *et al.* Submitted OCT-1992 to the EMBL GenBank DDBJ databases  
10 (ISOFORMS 3 AND 4); Mueller,S. *et al.* (1997) *J. Biol. Chem.* 272:24780-24793;  
Mueller,S. *et al.* (1999) *J. Biol. Chem.* 274:18165-18172; Engelmann,K. *et al.* (2001) *J.  
Biol. Chem.* 276:27764-27769; Baruch,A. *et al.* (1999) *Cancer Res.* 59:1552-1561);  
Parry,S. *et al.* (2001) *Biochem. Biophys. Res. Commun.* 283:715-720; Wreschner,D.H., *et  
al.* (2002) *Protein Sci.* 11:698-706; and Zrihan-Licht,S., *et al.* (1994) *FEBS Lett.* 356:130-  
15 136.

Mucin-1 (MUC1) is a type I membrane protein and contains 1 SEA domain. Two known secreted forms (5 and 9) are also produced. Mucin-1 may play a role in adhesive functions and in cell-cell interactions, metastasis and signaling. It may also provide a protective layer on epithelial surfaces. Direct or indirect interaction with actin  
20 cytoskeleton. Isoform 7 behaves as a receptor and binds the secreted isoform 5. The binding induces the phosphorylation of the isoform 7, alters cellular morphology and initiates cell signaling. Additionally, Isoform 7 can bind to grb2 adapter protein. The cleaved form of Mucin-1 (isoform 1) forms a tight heterodimer with the released C-terminal peptide (which is first secreted to be extracellular). MUC1 is expressed on ductal  
25 epithelial cells and on activated T-cells. Aberrantly glycosylated forms are expressed in human epithelial tumors, such as breast or ovarian cancer and also in non-epithelial tumor cells. Isoform 7 is expressed only in tumoral cells.

MUC1 is highly glycosylated (N-and O-linked carbohydrates and sialic acid). In the 20 amino acid tandem repeat positions 5 (ser), 6 (thr), 14 (thr), 15 (ser) and 19 (thr) are  
30 O-glycosylated (galnac). The average density of O-glycosylated sites within repeat peptides varies with cell differentiation from about 50% in lactation-associated MUC1 to over 90% in a variety of breast cancer cells. Isoforms 1 and 7 undergo transphosphorylation on serine and tyrosine residues.

The MUC1 number of repeats is highly polymorphic. It varies from 21 to 125 in the northern european population. The most frequent alleles contains 41 and 85 repeats. The tandemly repeated icosapeptide underlies polymorphism at three positions: PAPGSTAP[PAQT]AHGVTsap[DT/ES]R, DT -> ES and the single replacements P -> A, P -> Q and P-> T. The most frequent replacement DT > ES occurs in up to 50% of the repeats. SWISS-PROT accession Numbers: P15941, P13931, P15942, P17626, Q14128, Q14876, Q16437, Q16442, Q16615, Q9BXA4, Q9UE75, Q9UE76, Q9UQL1, Q9Y4J2. SWISS-PROT is accessible at <http://www.ebi.ac.uk/swissprot/>.

*Splice Variant Nucleotides*

10 Novel splice variants have been identified for the Mam096 family, DEX0432\_035.nt.1 and DEX0432\_036.nt.1 – DEX0432\_036.nt.48. These novel transcripts are located in the same genomic region as MUC1 family. Mam096 variants contain novel exon additions and deletions which encode for unique amino acid sequences. These unique amino acid sequence provide new proteins to be targeted for the 15 generation of reagents that can be used in the detection and/or treatment of cancer. The unique nucleotide sequences in these new transcript can be used as nucleic acid probes for the diagnosis and/or treatment of cancer.

Alignments of the DNA sequences for Mam096 family display regions of similarity and difference between transcripts.

20 *Splice Variant Polypeptides*

The nucleotide sequences of the novel splice variants for Mam096 (DEX0432\_035.nt.1 and DEX0432\_036.nt.1 – DEX0432\_036.nt.48), encode novel amino acid sequences DEX0432\_35.aa.1 and DEX0432\_36.aa.2 – DEX0432\_36.aa.46. The novel amino acid sequences are novel Mam096 protein variants. These proteins 25 contain novel features including unique epitopes, new cellular localizations, and altered function. Novel features of the proteins can be targeted for the generation of reagents that can be used in the detection and/or treatment of cancer.

Alignments of the amino acid sequences for Mam096 family display regions of similarity and difference between transcripts.

30 Altogether, splice variant sequence analysis, EST support, and SAGE tag data are indicative of SEQ ID NO: 1-94 and SEQ ID NO: 95-156 being a diagnostic marker and/or a therapeutic target for cancer.

**Example 1c: RT-PCR Analysis**

To detect the presence and tissue distribution of a particular splice variant Reverse Transcription-Polymerase Chain Reaction (RT-PCR) is performed using cDNA generated from a panel of tissue RNAs. See, e.g., Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press (1989) and; Kawasaki ES *et al.*, *PNAS* 85(15):5698 (1988). Total RNA is extracted from a variety of tissues and first strand cDNA is prepared with reverse transcriptase (RT). Each panel includes 23 cDNAs from five cancer types (lung, ovary, breast, colon, and prostate) and normal samples of testis, placenta and fetal brain. Each cancer set is composed of three cancer cDNAs from different donors and one normal pooled sample. Using a standard enzyme kit from BD Bioscience Clontech (Mountain View, CA), the target transcript is detected with sequence-specific primers designed to only amplify the particular splice variant. The PCR reaction is run on the GeneAmp PCR system 9900 (Applied Biosystem, Foster City, CA) thermocycler under optimal conditions. One of ordinary skill can design appropriate primers and determine optimal conditions. The amplified product is resolved on an agarose gel to detect a band of equivalent size to the predicted RT-PCR product. A band indicates the presence of the splice variant in a sample. The relation of the amplified product to the splice variant is subsequently confirmed by DNA sequencing.

The RT-PCR experiments confirm the physical existence of SEQ ID NO: 1-94 in a biological sample. RT-PCR experiments results include cancer tissue(s) detected in, predicted band length, and experimentally confirmed band length for each transcript.

RT-PCR results confirm the presence SEQ ID NO: 1-94 in biologic samples and distinguish between related transcripts.

**Example 1d: Secretion Assay**

To determine if a protein encoded by a novel splice variant is secreted from cells a secretion assay is preformed. pcDNA3.1 clones containing transcripts from the same family encoding different forms of proteins are transfected into 293T cells using the Superfect transfection reagent (Qiagen, Valencia CA). Transfected cells are incubated for 28 hours before the media is collected and immediately spun down to remove any detached cells. The adherent cells are solubilized with lysis buffer (1% NP40, 10mM sodium phosphate pH7.0, and 0.15M NaCl). The lysed cells are collected and spun down and the supernatant extracted as cell lysate. Western immunoblot is carried out in the

following manner: 15ul of the cell lysate and media are run on 4-12% NuPage Bis-Tris gel (Invitrogen, Carlsbad CA), and blotted onto a PVDF membrane (Invitrogen, Carlsbad CA). The blot is incubated with polyclonal anti-TRAILR2 primary antibody (Imgenex, San Diego CA) and polyclonal goat anti-rabbit-peroxidase secondary antibody (Sigma-Aldrich, St. Louis MO). The blot is developed with the ECL Plus chemiluminescent detection reagent (Amersham BioSciences, Piscataway NJ).

Secretion assay results are indicative of SEQ ID NO: 95-156 being a diagnostic marker and/or therapeutic target for cancer.

10   **Example 2A: Custom Microarray Experiment—Breast Cancer**

Custom oligonucleotide microarrays were provided by Agilent Technologies, Inc. (Palo Alto, CA). The microarrays were fabricated by Agilent using their technology for the in-situ synthesis of 60mer oligonucleotides (Hughes, et al. 2001, Nature Biotechnology 19:342-347). The 60mer microarray probes were designed by Agilent, from gene sequences provided by diaDexus, using Agilent proprietary algorithms. Whenever possible two different 60mers were designed for each gene of interest. All microarray experiments were two-color experiments and were performed using Agilent-recommended protocols and reagents. Briefly, each microarray was hybridized with cRNAs synthesized from polyA+ RNA, isolated from cancer and normal tissues, labeled with fluorescent dyes Cyanine3 and Cyanine5 (NEN Life Science Products, Inc., Boston, MA) using a linear amplification method (Agilent). In each experiment the experimental sample was polyA+ RNA isolated from cancer tissue from a single individual and the reference sample was a pool of polyA+ RNA isolated from normal tissues of the same organ as the cancerous tissue (i.e. normal breast tissue in experiments with breast cancer samples). Hybridizations were carried out at 60°C, overnight using Agilent in-situ hybridization buffer. Following washing, arrays were scanned with a GenePix 4000B Microarray Scanner (Axon Instruments, Inc., Union City, CA). The resulting images were analyzed with GenePix Pro 3.0 Microarray Acquisition and Analysis Software (Axon). A total of 29 experiments comparing the expression patterns of breast cancer derived polyA+ RNA (15 squamous cell carcinomas, 14 adenocarcinomas) to polyA+ RNA isolated from a pool of 12 normal breast tissues were analyzed.

Data normalization and expression profiling were done with Expressionist software from GeneData Inc. (Daly City, CA/Basel, Switzerland). Gene expression

analysis was performed using only experiments that meet certain quality criteria. The quality criteria that experiments must meet are a combination of evaluations performed by the Expressionist software and evaluations performed manually using raw and normalized data. To evaluate raw data quality, detection limits (the mean signal for a replicated negative control + 2 Standard Deviations (SD)) for each channel were calculated. The detection limit is a measure of non-specific hybridization. Arrays with poor detection limits were not analyzed and the experiments were repeated. To evaluate normalized data quality, positive control elements included in the array were utilized. These array features should have a mean ratio of 1 (no differential expression). If these features have a mean ratio of greater than 1.5-fold up or down, the experiments were not analyzed further and were repeated. In addition to traditional scatter plots demonstrating the distribution of signal in each experiment, the Expressionist software also has minimum thresholding criteria that employ user defined parameters to identify quality data. Only those features that meet the threshold criteria were included in the filtering and analyses carried out by Expressionist. The thresholding settings employed require a minimum area percentage of 60% [(% pixels > background + 2SD)-(% pixels saturated)], and a minimum signal to noise ratio of 2.0 in both channels. By these criteria, very low expressors and saturated features were not included in analysis.

Relative expression data was collected from Expressionist based on filtering and clustering analyses. Up- and down- regulated genes were identified using criteria for percentage of valid values obtained, and the percentage of experiments in which the gene is up- or down-regulated. These criteria were set independently for each data set, depending on the size and the nature of the data set. The results for the significantly upregulated and downregulated genes are shown in Table 1. The first three columns of the table contain information about the sequence itself (Oligo ID, Parent ID, and Patent#), the next 3 columns show the results obtained. '%valid' indicates the percentage of 29 unique experiments total in which a valid expression value was obtained, '%up' indicates the percentage of 29 experiments in which up-regulation of at least 2.5-fold was observed, and '%down' indicates the percentage of the 29 experiments in which down-regulation of at least 2.5-fold was observed. The last column in Table 1 describes the location of the microarray probe (oligo) relative to the parent sequence for upregulated genes. Table 2 describes the results and oligo locations for down-regulated genes. Tables 3 and 4 describe the results and oligo locations for up and down regulated genes, respectively.

Table 1. Sensitivity data for up-regulated genes. Data reported for Parent IDs (Par. ID) denoted by \* are calculated based on lower-voltage PMT scans due to saturation in higher-voltage PMT scans (extremely high expression levels).

5

DEX ID	Par. ID	% valid n=35	% up n=35	% up ST1 n=9	% up ST2, 3 n=26	Oligo ID	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEX S	Stop Pos. FLEX S
DEX0321_4	4787	27.8	11.1	33.3	3.7	11104	1497	1556		
DEX0321_4	4787	52.8	8.3	33.3	0	11105	1278	1337		
DEX0321_8	5572	100	38.9	33.3	40.7	21873	133	192		
DEX0321_14	5904	94.4	75	77.8	74.1	37806	18	77		
DEX0321_23	7407	86.1	30.6	11.1	37	26346	658	717	782	841
DEX0321_23	7407	63.9	2.8	0	3.7	26347	583	642	707	766
DEX0321_28	7689	77.8	50	55.6	48.1	12645	298	357		
DEX0321_28	7689	88.9	47.2	55.6	44.4	12646	270	329		
DEX0321_30	7951	97.2	8.3	11.1	7.4	15120	194	253		
DEX0321_30	7951	97.2	25	33.3	22.2	15121	101	160		
DEX0321_31	8181	100	41.7	22.2	48.1	17232	585	644	997	1056
DEX0321_31	8181	97.2	41.7	33.3	44.4	17233	371	430	783	842
DEX0321_33	8214	100	33.3	22.2	37	17942	178	237	446	505
DEX0321_33	8214	100	30.6	33.3	29.6	17943	120	179	388	447
DEX0321_35	8268	100	36.1	66.7	25.9	18206	571	630	572	631
DEX0321_35	8268	97.2	19.4	33.3	14.8	18207	211	270	211	270
DEX0321_38	8420	100	41.7	55.6	37	20235	973	1032		
DEX0321_38	8420	100	41.7	55.6	37	20236	707	766		
DEX0321_43	8644	94.4	36.1	33.3	37	26841	1431	1490		
DEX0321_44	8764	94.4	33.3	55.6	25.9	28227	1154	1213		
DEX0321_44	8764	58.3	11.1	22.2	7.4	28228	1056	1115		

Table 2. Sensitivity data for down-regulated genes. Data reported for Parent IDs denoted by \* are calculated based on lower-voltage PMT scans due to saturation in higher-voltage PMT scans (extremely high expression levels).

5

DEX ID	Par. ID	% valid n=35	% dn n=35	% dn ST1 n=9	% dn ST2, 3 n=26	Oligo ID	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0321_1	4259	100	30.6	33.3	29.6	20385	1398	1457		
DEX0321_1	4259	100	16.7	0	22.2	20386	1325	1384		
DEX0321_2	4507	100	33.3	44.4	29.6	17992	166	225		
DEX0321_2	4507	100	33.3	44.4	29.6	17993	146	205		
DEX0321_3	4560	100	33.3	55.6	25.9	23876	102	161		
DEX0321_5	4902	75	25	44.4	18.5	23856	789	848	789	848
DEX0321_5	4902	91.7	0	0	0	23857	646	705	646	705
DEX0321_7	5434	97.2	33.3	44.4	29.6	34823	289	348		
DEX0321_9	5640	86.1	36.1	22.2	40.7	41765	209	268		
DEX0321_10	5685	97.2	63.9	66.7	63	21328	160	219	692	751
DEX0321_12	5824	100	47.2	22.2	55.6	15681	152	211	2721	2780
DEX0321_12	5824	100	22.2	22.2	22.2	15682	126	185	2695	2754
DEX0321_15	5988	69.4	30.6	44.4	25.9	26124	347	406	654	713
DEX0321_15	5988	5.6	2.8	0	3.7	26125	306	365	613	672
DEX0321_17	6191	80.6	16.7	33.3	11.1	30141	121	180	283	342
DEX0321_19	6723	86.1	66.7	66.7	66.7	18882	654	713	654	713
DEX0321_19	6723	61.1	55.6	22.2	66.7	18883	610	669	610	669
DEX0321_21	6804	83.3	25	33.3	22.2	38921	582	641	633	692
DEX0321_21	6804	69.4	19.4	22.2	18.5	38922	451	510	502	561
DEX0321_25	7505*	100	36.1	22.2	38.5	15020	143	202		
DEX0321_25	7505*	100	33.3	22.2	38.5	15021	97	156		
DEX0321_27	7575	72.2	8.3	0	11.1	40479	76	135		
DEX0321_27	7575	100	69.4	55.6	74.1	40480	11	70		
DEX0321_29	7812	97.2	75	66.7	77.8	13936	144	203		
DEX0321_37	8376	94.4	0	0	0	19390	2438	2497		
DEX0321_37	8376	100	38.9	44.4	37	19391	2151	2210		
DEX0321	8476	97.2	2.8	11.1	0	20533	688	747	802	861

39											
DEX0321_39	8476	97.2	38.9	66.7	29.6	20534	590	649	704	763	
DEX0321_41	8502	97.2	27.8	11.1	33.3	20707	937	996	1749	1808	
DEX0321_41	8502	97.2	30.6	22.2	33.3	20708	897	956	1709	1768	
DEX0321_45	8936	88.9	63.9	55.6	66.7	31658	377	436	463	522	
DEX0321_45	8936	100	38.9	33.3	40.7	31659	256	315	342	401	
DEX0321_47	9072	94.4	11.1	33.3	3.7	33550	1310	1369			
DEX0321_47	9072	100	30.6	44.4	25.9	33551	742	801			

Table 3. Sensitivity data for stage-specific up-regulated genes.

DEX ID	Parent ID	%valid n=35	% up n=35	% up ST1 n=9	% up ST2,3 n=26	OligoID	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0321_4	4787	27.8	11.1	33.3	3.7	11104	1497	1556		
DEX0321_4	4787	52.8	8.3	33.3	0	11105	1278	1337		
DEX0321_23	7407	86.1	30.6	11.1	37	26346	658	717	782	841
DEX0321_23	7407	63.9	2.8	0	3.7	26347	583	642	707	766
DEX0321_35	8268	100	36.1	66.7	25.9	18206	571	630	572	631
DEX0321_35	8268	97.2	19.4	33.3	14.8	18207	211	270	211	270
DEX0321_44	8764	94.4	33.3	55.6	25.9	28227	1154	1213		
DEX0321_44	8764	58.3	11.1	22.2	7.4	28228	1056	1115		

5

Table 4. Sensitivity data for stage-specific down-regulated genes. Data reported for Parent IDs denoted by \* are calculated based on lower-voltage PMT scans due to saturation in higher-voltage PMT scans (extremely high expression levels).

10

DEX ID	Parent ID	%valid n=35	% dn n=35	% dn ST1 n=9	% dn ST2,3 n=26	OligoID	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0321_3	4560	100	33.3	55.6	25.9	23876	102	161		
DEX0321_5	4902	75	25	44.4	18.5	23856	789	848	789	848
DEX0321_5	4902	91.7	0	0	0	23857	646	705	646	705
DEX0321_12	5824	100	47.2	22.2	55.6	15681	152	211	2721	2780
DEX0321_12	5824	100	22.2	22.2	22.2	15682	126	185	2695	2754

**Example 2B: Relative Quantitation of Gene Expression**

Real-Time quantitative PCR with fluorescent Taqman® probes is a quantitation detection system utilizing the 5'- 3' nuclease activity of Taq DNA polymerase. The method uses an internal fluorescent oligonucleotide probe (Taqman®) labeled with a 5' reporter dye and a downstream, 3' quencher dye. During PCR, the 5'-3' nuclease activity

15

of Taq DNA polymerase releases the reporter, whose fluorescence can then be detected by the laser detector of the Model 7700 Sequence Detection System (PE Applied Biosystems, Foster City, CA, USA). Amplification of an endogenous control is used to standardize the amount of sample RNA added to the reaction and normalize for Reverse Transcriptase (RT) efficiency. Either cyclophilin, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATPase, or 18S ribosomal RNA (rRNA) is used as this endogenous control. To calculate relative quantitation between all the samples studied, the target RNA levels for one sample were used as the basis for comparative results (calibrator). Quantitation relative to the "calibrator" can be obtained using the comparative method (User Bulletin 10 #2: ABI PRISM 7900 Sequence Detection System).

The tissue distribution and the level of the target gene are evaluated for every sample in normal and cancer tissues. Total RNA is extracted from normal tissues, cancer tissues, and from cancers and the corresponding matched adjacent tissues. Subsequently, first strand cDNA is prepared with reverse transcriptase and the polymerase chain reaction 15 is done using primers and Taqman® probes specific to each target gene. The results are analyzed using the ABI PRISM 7900 Sequence Detector. The absolute numbers are relative levels of expression of the target gene in a particular tissue compared to the calibrator tissue.

One of ordinary skill can design appropriate primers. The relative levels of 20 expression of the BSNA versus normal tissues and other cancer tissues can then be determined. All the values are compared to the calibrator. Normal RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

The relative levels of expression of the BSNA in pairs of matched samples may 25 also be determined. A matched pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. All the values are compared to the calibrator.

In the analysis of matching samples, the BSNA show a high degree of tissue specificity for the tissue of interest. These results confirm the tissue specificity results 30 obtained with normal pooled samples. Further, the level of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual are compared. This comparison provides an indication of specificity for the cancer state (*e.g.* higher levels of mRNA expression in the cancer sample compared to the normal adjacent).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in matched samples tested are indicative of SEQ ID NO: XX(3) and the encoded protein SEQ ID NO: YY(3) being a diagnostic marker for cancer.

Mam097 (DEX0432\_028.nt.1)

5       The relative expression level of Mam097 in various tissue samples is included below. Tissue samples include 77 pairs of matching samples, 8 non matched cancer samples, and 36 normal samples, all from various tissues annotated in the table. A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. Of  
10      the normal samples 6 were blood samples which measured the expression level of the BSNA in blood cells. Additionally, 2 prostatitis, and 4 Benign Prostatic Hyperplasia (BPH) samples are included. All the values are compared to kidney normal sample KID55KD (calibrator).

15      The table below contains the relative expression level values for the sample as compared to the calibrator. The table includes the Sample Name, Tissue type, and expression level values for the following samples: Cancer (CAN), Normal Adjacent Tissue (NAT), Normal Tissue (NRM), Benign Prostatic Hyperplasia (BPH), and Prostatitis (PROST).

Sample	Tissue	CAN	NAT	NRM	BPH	PROST
mam522	Breast	689.05				
MamS854	Breast	264.37	228.55			
mamS516	Breast	1292.87	15.09			
mamS621	Breast	2741.5				
MamS570	Breast	0.17	86.76			
MamB011	Breast	17.7	155.21			
Mam19DN	Breast	115.71	115.97			
Mam781M	Breast	75.37	20.36			
MamS699	Breast	205.04	224.93			
Mam543M	Breast	8.17	5.58			
Mam976M	Breast	169.28	5.21			
MamS997	Breast	17.76	9.32			
mam355	Breast	274.93	20.02			
Mam42DN	Breast	236.57	51.85			
Mam76DN	Breast	1106.1	2.1			
Mam01MA	Breast			48.59		
Adr48AD	Adrenal			4.43		
Bld46XX	Bladder	24.18	24.72			
BldTR147	Bladder	14.44	8.12			
Bld520B	Bladder	110.07	45.07			
Bld23BL	Bladder			1.36		
BloB1	Blood			319.96		
BloB3	Blood			222.77		
BloB5	Blood			84.36		

BloB6	Blood		62.79		
BloB11	Blood		100.2		
BloB14	Blood		105.73		
Brn10BR	Brain		3.9		
CvxKS52	Cervix	1.37	12.79		
CvxKS83	Cervix	1.22	8.08		
CvxNKS18	Cervix	0.15	2.16		
CvxNKS81	Cervix	2.47	4.93		
CvxNKS54	Cervix	2.26	3.5		
Cvx1ACB	Cervix		0		
ClnAS43	Colon	0.81	3.98		
ClnAS98	Colon	1.49	1.82		
ClnRS53	Colon	0.84	4.82		
ClnRC01	Colon	6.62	2.98		
ClnSG27	Colon	0.8	11.92		
ClnDC19	Colon	8.99	22.93		
ClnDC63	Colon	6.28	29.18		
ClnCM12	Colon	6.07	8.07		
ClnTX01	Colon	2.7	9.37		
Cln01CL	Colon				
Endo10479	Endometrium	13.55	10.4		
Endo28XA	Endometrium	12.24	39.82		
Endo3AX	Endometrium	33.37	23.05		
Eso1ES	Esophagus		1.68		
Hrt46HR	Heart		0.46		
Kid11Xd	Kidney	28.03	2.34		
Kid109XD	Kidney	6.86	14.02		
Kid10XD	Kidney	27.44	0.03		
Kid124D	Kidney	7.68	2.08		
Kid126XD	Kidney	32.77	3.96		
KID55KD	Kidney		1		
Lvr15XA	Liver	1.75	2.25		
Lv4147L	Liver	8.51	7.91		
Lvr390L	Liver	6.81	1.32		
Liv89LV	Liver		690.81		
Lng354L	Lung	16.02	0		
Lng205L	Lung	2.2	21.32		
LngAC11	Lung	0	14.36		
LngAC39	Lung	17.43	56.6		
Lng315L	Lung	0	7.28		
LngSQ80	Lung	19.12	15.06		
Lng163L	Lung	0	4.21		
LngSQ81	Lung	0	0		
Lng507L	Lung	51.76	45.78		
LNG90LN	Lung		59.43		
Ovrg021	Ovary	0.48	0.89		
Ovr206I	Ovary		3.44		
Ovr20GA	Ovary		0		
Ovr18GA	Ovary		7.06		
Ovr3370	Ovary		8.64		
Ovr1230	Ovary		6.51		
Ovrc177	Ovary		5.63		
Ovr40G	Ovary		10.85		
Ovr10050	Ovary	13.69			
Ovr10400	Ovary	9.66			
Ovr1050	Ovary	29.1			
Ovr130X	Ovary	4.05			

OvrC004	Ovary			2.52		
Ovr63A	Ovary	11.08				
OvrA1B	Ovary	32.27				
Ovr3AOV	Ovary			18.58		
Pan77X	Pancreas	3	3.72			
Pan82XP	Pancreas	21.73	1.45			
Pan92X	Pancreas	20.53	46.03			
Pan35PA	Pancreas					
Pla59PL	Placenta			21.2		
Pro91X	Prostate	2.56	19.24			
Pro109XB	Prostate	0.93	24.15			
Pro134P	Prostate	67.94	56.6			
Pro34B	Prostate	16.65	12.36			
Pro326	Prostate	13.82	34.54			
Pro705P	Prostate			18.12		
Pro784P	Prostate			24.52		
Pro83P	Prostate			33.22		
Pro263C	Prostate			43.33		
Pro10R	Prostate			0		
Pro20R	Prostate			19.97		
Pro09PR	Prostate			98.67		
Rec21RC	Rectum			0		
Skn248S	Skin	23.15	6.33			
Skn287S	Skin	1.66	32.07			
Skn669S	Skin	22.19	23.83			
Ms184MU	Sktl. Muscle			0.83		
SmInt21XA	Sm. Intestine	47.45	21.79			
SmIntH89A	Sm. Intestine	6.76	16.35			
SmInt20SM	Sm. Intestine	27.43	14.28			
SmInt01SM	Sm. Intestine			7.13		
Spl7GSP	Spleen			4.58		
Sto88S	Stomach	14.72	8.2			
Sto261S	Stomach	10.22	8.61			
Sto288S	Stomach	16.51	0			
StoMT54	Stomach	0.28	2.38			
Sto09ST	Stomach			0.51		
Tst39X	Testis	27.45	8.34			
Tst647T	Testis	36.43	7.8			
Tst663T	Testis	37.5	2.93			
Tst4GTS	Testis			0		
Thy99TM	Thymus			101.8		
Thrd56T	Thyroid	21.99	3.99			
Thrd143N	Thyroid	71.17	23.53			
Thrd270T	Thyroid	0.32	3.43			
Tra16TR	Trachea			25.5		
Utr135XO	Uterus	52.33	49.72			
Utr85XU	Uterus	50.57	65.74			
Utr57UT	Uterus			36.7		

0.00= Negative

The sensitivity for Mam097 expression was calculated for the cancer samples versus normal samples and for the cancer samples versus the expression in the normal adjacent tissue from the same patient. The sensitivity value indicates the percentage of cancer samples that show levels of Mam097 at least 2 fold higher than the normal tissue or

the corresponding normal adjacent form the same patient. Sensitivity data is reported in the table below.

Sensitivity	Breast
≥ 2 fold Up-regulated vs. NAT	53.3%
≥ 2 fold Up-regulated vs. NRM	66.7%

The breast tissue specificity for Mam097 is of 66.7%. This specificity is an  
5 indication of the level of breast tissue specific expression of the transcript compared to all the other tissue types tested in our assay. Thus, these experiments indicate Mam097 being useful as a breast cancer diagnostic and/or therapeutic marker.

Altogether, the tissue specificity, plus the mRNA differential expression in the samples tested are believed to make Mam097 a good marker for diagnosing, monitoring,  
10 staging, imaging and treating breast cancer.

Primers used for QPCR Expression Analysis of Mam097 are as follows:

SEQ ID NO: 157 (Mam097\_probe): CACTTCCTTTAGTTTGCCTGG

SEQ ID NO: 158 (Mam097\_forward): ATCCTGAATTCTGAGACCATCCA

SEQ ID NO: 159 (Mam097\_reverse): GCCTCCAGCACACTCTTCAGT

15 Mam106 (DEX0432\_030.nt.1)

The relative expression level of Mam106 in various tissue samples is included below. Tissue samples include 77 pairs of matching samples, 8 non matched cancer samples, and 36 normal samples, all from various tissues annotated in the table. A matching pair is formed by mRNA from the cancer sample for a particular tissue and  
20 mRNA from the normal adjacent sample for that same tissue from the same individual. Of the normal samples 6 were blood samples which measured the expression level of the BSNA in blood cells. Additionally, 2 prostatitis, and 4 Benign Prostatic Hyperplasia (BPH) samples are included. All the values are compared to bladder cancer sample Bld46XK (calibrator).

25 The table below contains the relative expression level values for the sample as compared to the calibrator. The table includes the Sample Name, Tissue type, and expression level values for the following samples: Cancer (CAN), Normal Adjacent Tissue (NAT), Normal Tissue (NRM), Benign Prostatic Hyperplasia (BPH), and Prostatitis (PROST).

Sample	Tissue	CAN	NAT	NRM	BPH	PROST
Mam01MA	Breast			0.02		
Mam19DN	Breast	7.35	0.33			

mam355	Breast		0.01			
Mam42DN	Breast					
mam522	Breast	0.08	0.04			
Mam543M	Breast		0.15			
Mam76DN	Breast	0.18	0.11			
Mam781M	Breast	1.89	0.34			
Mam976M	Breast					
MamB011	Breast	0.06	0.21			
mamS516	Breast	0.14	0.02			
MamS570	Breast	3.56	0.88			
mamS621	Breast	1.00	0.01			
MamS699	Breast	1.02	0.25			
MamS854	Breast	1.52	1.49			
MamS997	Breast	0.42	0.36			
Adr48AD	Adrenal			0.16		
Bld23BL	Bladder					
Bld46XK	Bladder	0.94	0.74			
Bld520B	Bladder	2.52	0.31			
BldTR147	Bladder	1.67				
BloB1	Blood			2.32		
BloB11	Blood			5.16		
BloB14	Blood			9.71		
BloB3	Blood			0.44		
BloB5	Blood			1.31		
BloB6	Blood			0.46		
Brn10BR	Brain					
Cvx1ACB	Cervix			8.64		
CvxKS52	Cervix	0.17				
CvxKS83	Cervix	1.42	0.85			
CvxNKS18	Cervix	2.40	0.67			
CvxNKS54	Cervix	16.62	0.77			
CvxNKS81	Cervix	0.62	2.28			
Cln01CL	Colon			0.02		
ClnAS43	Colon	1.65	0.49			
ClnAS98	Colon	4.49	0.45			
ClnCM12	Colon	0.14	0.50			
ClnDC19	Colon	0.70	0.61			
ClnDC63	Colon	1.50	1.23			
ClnRC01	Colon	0.82	0.23			
ClnRS53	Colon	0.23	1.08			
ClnSG27	Colon	0.35	0.40			
ClnTX01	Colon	0.46	0.44			
Endo10479	Endometrium	0.65	3.87			
Endo28XA	Endometrium	2.85	1.68			
Endo3AX	Endometrium	0.33	0.97			
Eso1ES	Esophagus			0.24		
Hrt46HR	Heart					
Kid109XD	Kidney	1.68	0.52			
Kid10XD	Kidney	0.13	0.12			
Kid11Xd	Kidney	0.49	0.28			
Kid124D	Kidney	3.55	0.83			
Kid126XD	Kidney	0.45	0.15			
Kid55KD	Kidney			0.02		
Liv89LV	Liver			0.01		
Lv4147L	Liver	0.23	0.32			
Lvr15XA	Liver	1.59	0.73			
Lvr390L	Liver	0.92	0.59			

Lng163L	Lung	1.62	0.27			
Lng205L	Lung	1.07	0.74			
Lng315L	Lung	1.24	0.78			
Lng354L	Lung	0.59				
Lng507L	Lung	1.22	1.85			
Lng90LN	Lung			0.33		
LngAC11	Lung	0.84	1.19			
LngAC39	Lung	0.71	1.51			
LngSQ80	Lung	6.76	1.16			
LngSQ81	Lung	0.33	0.28			
Ovr1005O	Ovary	0.57				
Ovr1040O	Ovary	0.85				
Ovr105O	Ovary	1.49				
Ovr123O	Ovary			1.07		
Ovr130X	Ovary	1.41				
Ovr18GA	Ovary			0.98		
Ovr206I	Ovary			1.06		
Ovr20GA	Ovary			0.31		
Ovr337O	Ovary			2.17		
Ovr3AOV	Ovary			0.12		
Ovr40G	Ovary			0.99		
Ovr63A	Ovary	0.50				
OvrA1B	Ovary	2.25				
OvrC004	Ovary			3.96		
OvrC177	Ovary			0.47		
OvrG021	Ovary	1.20	1.56			
Pan35PA	Pancreas			0.30		
Pan77X	Pancreas	1.43	0.95			
Pan82XP	Pancreas	0.78	9.90			
Pan92X	Pancreas	1.96	1.31			
Pla59PL	Placenta			0.74		
Pro09PR	Prostate			0.45		
Pro109XB	Prostate	1.85	22.06			
Pro10R	Prostate					
Pro134P	Prostate	7.81	11.88			
Pro20R	Prostate					
Pro263C	Prostate			1.25		
Pro326	Prostate	6.02	2.04			
Pro34B	Prostate	20.81	9.46			
Pro705P	Prostate			2.62		
Pro784P	Prostate			7.35		
Pro83P	Prostate			1.13		
Pro91X	Prostate	3.22	3.76			
Rec21RC	Rectum					
Skn248S	Skin	2.91	0.59			
Skn287S	Skin	1.34	5.85			
Skn669S	Skin	0.21				
Ms184MU	Sktl. Muscle					
SmInt01SM	Sm. Intestine			1.07		
SmInt20SM	Sm. Intestine			0.90		
SmInt21XA	Sm. Intestine	1.61	0.80			
SmIntH89A	Sm. Intestine	0.74	0.45			
Spl7GSP	Spleen			0.09		
Sto09ST	Stomach			0.20		
Sto261S	Stomach	2.80	1.72			
Sto288S	Stomach	0.55	3.35			
Sto88S	Stomach	1.61	2.15			

StoMT54	Stomach	1.04	1.75			
Tst39X	Testis	0.58	2.06			
Tst4GTS	Testis					
Tst647T	Testis	1.74	0.32			
Tst663T	Testis	1.69				
Thy99TM	Thymus					
Thrd143N	Thyroid	2.30	1.04			
Thrd270T	Thyroid	0.69	0.62			
Thrd56T	Thyroid	4.42	1.06			
Tra16TR	Trachea			3.46		
Utr135XO	Uterus	0.24	1.66			
Utr57UT	Uterus			3.03		
Utr85XU	Uterus	2.33	1.95			

0.00= Negative

The sensitivity for Mam106 expression was calculated for the cancer samples versus normal samples and for the cancer samples versus the expression in the normal adjacent tissue from the same patient. The sensitivity value indicates the percentage of cancer samples that show levels of Mam106 at least 2 fold higher than the normal tissue or the corresponding normal adjacent form the same patient. Sensitivity data is reported in the table below.

Sensitivity	Breast
≥ 2 fold Up-regulated vs. NAT	50%
≥ 2 fold Up-regulated vs. NRM	79%

10 The breast tissue specificity for Mam106 is of 10%. This specificity is an indication of the level of breast tissue specific expression of the transcript compared to all the other tissue types tested in our assay. Thus, these experiments indicate Mam106 being useful as a breast cancer diagnostic and/or therapeutic marker.

15 Altogether, the tissue specificity, plus the mRNA differential expression in the samples tested are believed to make Mam106 a good marker for diagnosing, monitoring, staging, imaging and treating breast cancer.

Primers used for QPCR Expression Analysis of Mam106 are as follows:

SEQ ID NO: 160 (Mam106\_probe): AGCCGGAGGAGATGTGGCTCTACCG

SEQ ID NO: 161 (Mam106\_forward): CCGCTTCCCCAGAGACTCATC

20 SEQ ID NO: 162 (Mam106\_reverse): GCACAAACATCGGCTTGGT

#### Mam096 (DEX0432\_035.nt.1; DEX0432\_036.nt.1 - DEX0432\_036.nt.48)

The relative expression level of Mam096 in various tissue samples is included below. Tissue samples include 77 pairs of matching samples, 8 non matched cancer samples, and 36 normal samples, all from various tissues annotated in the table. A

matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. Of the normal samples 6 were blood samples which measured the expression level of the BSNA in blood cells. Additionally, 2 prostatitis, and 4 Benign Prostatic Hyperplasia (BPH) samples are included. All the values are compared to breast cancer sample 5 mamS621 (calibrator).

The table below contains the relative expression level values for the sample as compared to the calibrator. The table includes the Sample Name, Tissue type, and expression level values for the following samples: Cancer (CAN), Normal Adjacent 10 Tissue (NAT), Normal Tissue (NRM), Benign Prostatic Hyperplasia (BPH), and Prostatitis (PROST).

Sample	Tissue	CAN	NAT	NRM	BPH	PROST
Mam01MA	Breast			1.75		
Mam19DN	Breast	3.84	0.00			
mam355	Breast	1.00	0.004			
Mam42DN	Breast		0.00			
mam522	Breast	0.04	0.00			
Mam543M	Breast	2.26	0.00			
Mam76DN	Breast	0.06	0.00			
Mam781M	Breast		1.53			
Mam976M	Breast		0.00			
MamB011	Breast	0.50	0.62			
mamS516	Breast		0.00			
MamS570	Breast	13.56	0.00			
mamS621	Breast	1.00	0.00			
MamS699	Breast	0.93	0.00			
MamS854	Breast		0.00			
MamS997	Breast		0.00			
Adr48AD	Adrenal			0.00		
Bld23BL	Bladder					
Bld46XK	Bladder	0.00	52.72			
Bld520B	Bladder	0.00	0.00			
BldTR147	Bladder	9.39	0.00			
Blob1	Blood			0.00		
Blob11	Blood			0.00		
Blob14	Blood			0.00		
Blob3	Blood			0.00		
Blob5	Blood			0.00		
Blob6	Blood			0.00		
Brn10BR	Brain			0.00		
Cvx1ACB	Cervix			0.00		
CvxKS52	Cervix	0.00	0.00			
CvxKS83	Cervix	0.00	0.00			
CvxNKS18	Cervix	4.38	0.00			
CvxNKS54	Cervix	7.72	0.00			
CvxNKS81	Cervix	0.00	0.00			
Cln01CL	Colon			0.20		
ClnAS43	Colon	6.96	1.64			
ClnAS98	Colon	3.04	0.00			

ClnCM12	Colon	0.55	0.00			
ClnDC19	Colon	0.65	0.00			
ClnDC63	Colon	2.07	0.00			
ClnRC01	Colon	0.00	0.00			
ClnRS53	Colon	0.00	0.00			
ClnSG27	Colon	2.55	3.07			
ClnTX01	Colon	0.00	2.41			
Endo10479	Endometrium	5.22	0.00			
Endo28XA	Endometrium	7.02	9.74			
Endo3AX	Endometrium	0.00	0.00			
Esoles	Esophagus			0.00		
Hrt46HR	Heart			0.00		
Kid109XD	Kidney	1.25	1.31			
Kid10XD	Kidney	0.52	0.00			
Kid11Xd	Kidney	0.22	3.08			
Kid124D	Kidney	0.00	4.62			
Kid126XD	Kidney	0.00	3.64			
Kid55KD	Kidney			0.04		
Liv89LV	Liver			0.00		
Lv4147L	Liver	0.00	0.00			
Lvr15XA	Liver	0.00	0.00			
Lvr390L	Liver	18.15	0.00			
Lng163L	Lung	0.00	0.00			
Lng205L	Lung	3.50	91.36			
Lng315L	Lung	0.00	0.00			
Lng354L	Lung	0.00	0.00			
Lng507L	Lung	67.15	10.06			
Lng90LN	Lung			0.21		
LngAC11	Lung	21.28	19.12			
LngAC39	Lung	61.63	0.00			
LngSQ80	Lung	5.45	21.39			
LngSQ81	Lung	15.42	131.51			
Ovr10050	Ovary	73.79				
Ovr10400	Ovary	6.69				
Ovr1050	Ovary	54.02				
Ovr1230	Ovary			0.00		
Ovr130X	Ovary	118.65				
Ovr18GA	Ovary			0.00		
Ovr206I	Ovary			1.22		
Ovr20GA	Ovary			0.00		
Ovr3370	Ovary			0.00		
Ovr3AOV	Ovary			0.00		
Ovr40G	Ovary			0.00		
Ovr63A	Ovary	0.00				
OvrA1B	Ovary	1257.69				
Ovrc004	Ovary			0.00		
Ovrc177	Ovary			0.00		
Ovrg021	Ovary	28.86	0.00			
Pan35PA	Pancreas			0.47		
Pan77X	Pancreas	0.00	0.00			
Pan82XP	Pancreas	0.18	0.00			
Pan92X	Pancreas	292.34	0.00			
Pla59PL	Placenta			0.00		
Pro09PR	Prostate			0.04		
Pro109XB	Prostate	0.00	0.00			
Pro10R	Prostate				0.00	
Pro134P	Prostate	0.00	0.00			

Pro20R	Prostate				0.00
Pro263C	Prostate			0.00	
Pro326	Prostate	0.00	0.00		
Pro34B	Prostate	0.00	0.00		
Pro705P	Prostate			0.00	
Pro784P	Prostate			0.00	
Pro83P	Prostate			0.00	
Pro91X	Prostate	0.00	0.00		
Rec21RC	Rectum			0.00	
Skn248S	Skin	0.00	0.00		
Skn287S	Skin	0.00	0.00		
Skn669S	Skin	0.00	0.00		
Ms184MU	Sktl. Muscle			0.00	
SmInt01SM	Sm. Intestine			0.00	
SmInt20SM	Sm. Intestine	0.00	0.00		
SmInt21XA	Sm. Intestine	0.00	0.00		
SmIntH89A	Sm. Intestine	12.43	0.00		
Spl7GSP	Spleen			0.27	
Sto09ST	Stomach			0.20	
Sto261S	Stomach	0.00	0.00		
Sto288S	Stomach	32.51	0.00		
Sto88S	Stomach	0.00	5.74		
StoMT54	Stomach	7.37	0.00		
Tst39X	Testis	0.00	0.00		
Tst4GTS	Testis			0.00	
Tst647T	Testis	0.00	0.00		
Tst663T	Testis	0.00	0.00		
Thy99TM	Thymus			0.00	
Thrd143N	Thyroid	0.00	0.00		
Thrd270T	Thyroid	1.32	1.77		
Thrd56T	Thyroid	0.00	0.00		
Tra16TR	Trachea			0.00	
Utr135XO	Uterus	1.92	2.26		
Utr57UT	Uterus			0.00	
Utr85XU	Uterus	10.00	0.00		

0.00= Negative

The sensitivity for Mam096 expression was calculated for the cancer samples versus normal samples and for the cancer samples versus the expression in the normal adjacent tissue from the same patient. The sensitivity value indicates the percentage of cancer samples that show levels of Mam096 at least 2 fold higher than the normal tissue or the corresponding normal adjacent form the same patient. Sensitivity data is reported in the table below.

Sensitivity	Breast
≥ 2 fold Up-regulated vs. NAT	53%
≥ 2 fold Up-regulated vs. NRM	13%

10 The breast tissue specificity for Mam096 is of 49%. This specificity is an indication of the level of breast tissue specific expression of the transcript compared to all

the other tissue types tested in our assay. Thus, these experiments indicate Mam096 being useful as a breast cancer diagnostic and/or therapeutic marker.

Altogether, the tissue specificity, plus the mRNA differential expression in the samples tested are believed to make Mam096 a good marker for diagnosing, monitoring, 5 staging, imaging and treating breast cancer.

Primers used for QPCR Expression Analysis of Mam096 are as follows:

SEQ ID NO: 163 (Mam096\_probe): AGAGAGACATTTCTGAAATGGCTGTCT

SEQ ID NO: 164 (Mam096\_forward): CCCAGCACCGACTACTACCAA

SEQ ID NO: 165 (Mam096\_reverse): AGCTGCCCGTAGTTCTTCG

10 Mam103 (DEX0432\_038.nt.1)

The relative expression level of Mam103 in various tissue samples is included below. Tissue samples include 74 pairs of matching samples, 7 non matched cancer samples, and 38 normal samples, all from various tissues annotated in the table. A matching pair is formed by mRNA from the cancer sample for a particular tissue and 15 mRNA from the normal adjacent sample for that same tissue from the same individual. Of the normal samples 6 were blood samples which measured the expression level of the BSNA in blood cells. Additionally, 2 prostatitis, and 4 Benign Prostatic Hyperplasia (BPH) samples are included. All the values are compared to breast normal adjacent sample Mam522 (calibrator).

20 The table below contains the relative expression level values for the sample as compared to the calibrator. The table includes the Sample Name, Tissue type, and expression level values for the following samples: Cancer (CAN), Normal Adjacent Tissue (NAT), Normal Tissue (NRM), Benign Prostatic Hyperplasia (BPH), and Prostatitis (PROST).

Sample	Tissue	CAN	NAT	NRM	BPH	PROST
Mam01MA	Breast			0.00		
Mam19DN	Breast	0.04	0.00			
Mam42DN	Breast	0.00	0.00			
Mam522	Breast		1.00			
Mam543M	Breast	N/A	0.01			
Mam781M	Breast	0.15	0.02			
Mam976M	Breast	0.05	0.00			
MamS516	Breast	0.20				
MamS570	Breast	0.00	0.00			
MamS699	Breast	0.01	0.00			

MamS854	Breast	0.00	0.00			
MamS997	Breast	0.01	0.00			
Adr48AD	Adrenal			0.00		
Bld23BL	Bladder			0.00		
Bld46XK	Bladder	0.11	0.05			
Bld520B	Bladder	0.11	0.03			
BldTR147	Bladder	0.15	0.00			
BloB1	Blood			1.73		
BloB11	Blood			2.49		
BloB14	Blood			0.42		
BloB3	Blood			0.95		
BloB5	Blood			0.43		
BloB6	Blood			0.42		
Brn10BR	Brain			0.00		
Cvx1ACB	Cervix			0.18		
CvxKS52	Cervix	0.01	0.00			
CvxKS83	Cervix	0.39	0.00			
CvxNKS18	Cervix	0.08	0.08			
CvxNKS54	Cervix	0.09	0.00			
CvxNKS81	Cervix	0.09	0.00			
Cln01CL	Colon			0.00		
ClnAS43	Colon	0.02	0.00			
ClnAS98	Colon	0.02	0.00			
ClnCM12	Colon	0.00	0.01			
ClnDC19	Colon	0.01	0.09			
ClnDC63	Colon	0.01	0.02			
ClnRC01	Colon	0.00	0.00			
ClnRS53	Colon	0.00	0.01			
ClnSG27	Colon	0.00	0.02			
ClnTX01	Colon	0.01	0.00			
Endo10479	Endometrium	0.15	0.00			
Endo28XA	Endometrium	0.03	0.03			
Endo3AX	Endometrium	0.02	0.05			
Eso1ES	Esophagus			0.00		
Hrt46HR	Heart			0.00		
Kid109XD	Kidney	0.02	0.02			
Kid10XD	Kidney	0.00	0.00			
Kid11Xd	Kidney	0.11	0.04			
Kid124D	Kidney	0.02	0.00			
Kid126XD	Kidney	0.05	0.00			
Kid55KD	Kidney			0.02		
Liv89LV	Liver			0.00		
Lv4147L	Liver	0.00	0.00			
Lvr15XA	Liver	0.00	0.01			
Lvr390L	Liver	0.09	0.00			
Lng163L	Lung	0.05	0.00			
Lng205L	Lung	0.00	0.00			

Lng315L	Lung	0.02	0.00			
Lng354L	Lung	0.00	0.00			
Lng507L	Lung	0.03	0.00			
Lng90LN	Lung			0.14		
LngAC11	Lung	0.02	0.00			
LngAC39	Lung	0.02	0.00			
LngSQ80	Lung	0.00	0.04			
LngSQ81	Lung	0.01	0.01			
Ovr1005O	Ovary	0.02				
Ovr1040O	Ovary	0.00				
Ovr105O	Ovary	0.02				
Ovr1230	Ovary			0.00		
Ovr130X	Ovary	0.03				
Ovr18GA	Ovary			0.12		
Ovr206I	Ovary			0.04		
Ovr20GA	Ovary			0.03		
Ovr3370	Ovary			0.07		
Ovr3AOV	Ovary			0.00		
Ovr40G	Ovary			0.04		
Ovr63A	Ovary	0.02				
OvRA1B	Ovary	0.08				
OvrC004	Ovary			0.22		
OvrC177	Ovary			0.06		
OvrG021	Ovary	0.02	0.00			
Pan35PA	Pancreas			0.00		
Pan77X	Pancreas	0.00	0.00			
Pan82XP	Pancreas	0.02	0.81			
Pan92X	Pancreas	0.00	0.02			
Pla59PL	Placenta			0.02		
Pro09PR	Prostate			0.00		
Pro109XB	Prostate	0.01	0.04			
Pro10R	Prostate				0.00	
Pro134P	Prostate	0.04	0.05			
Pro20R	Prostate				N/A	
Pro263C	Prostate			0.06		
Pro326	Prostate	0.01	0.01			
Pro34B	Prostate	0.00	0.00			
Pro705P	Prostate			0.00		
Pro784P	Prostate			0.03		
Pro83P	Prostate			0.00		
Pro91X	Prostate	0.00	0.00			
Rec21RC	Rectum			0.00		
Skn248S	Skin	0.14	0.00			
Skn287S	Skin	0.01	0.00			
Skn669S	Skin	0.00	0.00			
Ms184MU	Sktl. Muscle			0.00		
SmInt01SM	Sm. Instestine			0.00		

SmInt20SM	Sm. Intestine	0.00	0.00			
SmInt21XA	Sm. Intestine	0.00	0.00			
SmIntH89A	Sm. Intestine	0.05	0.02			
Spl7GSP	Spleen			0.02		
Sto09ST	Stomach			0.00		
Sto261S	Stomach	0.08	0.00			
Sto288S	Stomach	0.02	1.12			
Sto88S	Stomach	0.00	0.00			
StoMT54	Stomach	0.02	0.02			
Tst39X	Testis	0.16	0.01			
Tst4GTS	Testis			0.00		
Tst647T	Testis	0.02	0.01			
Tst663T	Testis	0.06	0.01			
Thy99TM	Thymus			0.00		
Thrd143N	Thyroid	0.01	0.00			
Thrd270T	Thyroid	0.01	0.00			
Thrd56T	Thyroid	0.00	0.22			
Tra16TR	Trachea			0.00		
Utr135XO	Uterus	0.01	0.01			
Utr57UT	Uterus			0.00		
Utr85XU	Uterus	0.03	0.02			

0.00= Negative

The sensitivity for Mam103 expression was calculated for the cancer samples versus normal samples and for the cancer samples versus the expression in the normal adjacent tissue from the same patient. The sensitivity value indicates the percentage of cancer samples that show levels of Mam103 at least 2 fold higher than the normal tissue or the corresponding normal adjacent form the same patient. Sensitivity data is reported in the table below.

Sensitivity	Breast
≥ 2 fold Up-regulated vs. NAT	79%
≥ 2 fold Up-regulated vs. NRM	63%

10 The breast tissue specificity for Mam103 is of 42%. This specificity is an indication of the level of breast tissue specific expression of the transcript compared to all the other tissue types tested in our assay. Thus, these experiments indicate Mam103 being useful as a breast cancer diagnostic and/or therapeutic marker.

15 Altogether, the tissue specificity, plus the mRNA differential expression in the samples tested are believed to make Mam103 a good marker for diagnosing, monitoring, staging, imaging and treating breast cancer.

Primers used for QPCR Expression Analysis of Mam103 are as follows:

SEQ ID NO: 166 (Mam103\_probe): CTGAAAGCAGGTCACCCCTGAGATCCT

SEQ ID NO: 167 (Mam103\_forward): CAGAGCTTGGCCAGGTTCTAA

SEQ ID NO: 169 (Mam103\_reverse): TGCTAGGGTGCCCCTCTGT

Mam098 (DEX0432\_044.nt.1)

5 The relative expression level of Mam098 in various tissue samples is included below. Tissue samples include 6 pairs of matching samples, and 11 normal samples, all from various tissues annotated in the table. A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. All the values are compared to breast cancer sample  
10 Mam76DN (calibrator).

The table below contains the relative expression level values for the sample as compared to the calibrator. The table includes the Sample Name, Tissue type, and expression level values for the following samples: Cancer (CAN), Normal Adjacent Tissue (NAT), Normal Tissue (NRM).

Sample	Tissue	CAN	NAT	NRM
Mam01MA	Mammary			0.03
mam355	Mammary	0.07	0.01	
MamB011	Mammary	0.00	0.22	
mamS621	Mammary	0.47	0.00	
mamS516	Mammary	0.19	0.00	
mam522	Mammary	0.45	0.01	
Mam76DN	Mammary	1.00	0.05	
Bld23BL	Bladder			0.00
Cln01CL	Colon			0.01
Kid55KD	Kidney			0.00
Liv89LV	Liver			0.01
Lng90LN	Lung			0.01
Ovr3AOV	Ovary			0.00
Pan35PA	Pancreas			0.00
Pro09PR	Prostate			0.06
Spl7GSP	Spleen			0.03
Sto09ST	Stomach			0.00

15 0.00= Negative

The tissue specificity, plus the mRNA differential expression in the samples tested are believed to make Mam098 a good marker for diagnosing, monitoring, staging, imaging and treating breast cancer.

20 Primers used for QPCR Expression Analysis of Mam098 are as follows:

SEQ ID NO: 169 (Mam098\_probe): CCTTTAGGGCCTGGGACAACCACG

SEQ ID NO: 170 (Mam098\_forward): TGGATAACAAGCCCACAAATGA

SEQ ID NO: 171 (Mam098\_reverse): CCTCTAGTCCAGCCCCTTTAG

5   **Example 3: Protein Expression**

The BSNA is amplified by polymerase chain reaction (PCR) and the amplified DNA fragment encoding the BSNA is subcloned in pET-21d for expression in *E. coli*. In addition to the BSNA coding sequence, codons for two amino acids, Met-Ala, flanking the NH<sub>2</sub>-terminus of the coding sequence of BSNA, and six histidines, flanking the 10 COOH-terminus of the coding sequence of BSNA, are incorporated to serve as initiating Met/restriction site and purification tag, respectively.

An over-expressed protein band of the appropriate molecular weight may be observed on a Coomassie blue stained polyacrylamide gel. This protein band is confirmed by Western blot analysis using monoclonal antibody against 6X Histidine tag.

15       Large-scale purification of BSP is achieved using cell paste generated from 6-liter bacterial cultures, and purified using immobilized metal affinity chromatography (IMAC). Soluble fractions that are separated from total cell lysate were incubated with a nickle chelating resin. The column is packed and washed with five column volumes of wash buffer. BSP is eluted stepwise with various concentration imidazole buffers.

20   **Example 4: Fusion Proteins**

The human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector. For example, if pC4 (Accession No. 25 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 2, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a 30 fusion protein will not be produced. If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if

the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. *See, e. g.*, WO 96/34891.

#### **Example 5: Production of an Antibody from a Polypeptide**

In general, such procedures involve immunizing an animal (preferably a mouse) 5 with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100, µg/ml of streptomycin. The 10 splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP20), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands *et al.*, 15 *Gastroenterology* 80: 225-232 (1981).

The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide. Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that 20 antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific 25 antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

The polypeptides of the present invention were analyzed and the following attributes were identified; specifically, epitopes, post translational modifications, signal 30 peptides and transmembrane domains. Antigenicity (Epitope) prediction was performed through the antigenic module in the EMBOSS package. Rice, P., EMBOSS: The European Molecular Biology Open Software Suite, *Trends in Genetics* 16(6): 276-277

- (2000). The antigenic module predicts potentially antigenic regions of a protein sequence, using the method of Kolaskar and Tongaonkar. Kolaskar, AS and Tongaonkar, PC., A semi-empirical method for prediction of antigenic determinants on protein antigens, *FEBS Letters* 276: 172-174 (1990). Examples of post-translational modifications (PTMs) and other motifs of the \*\*\*XSP\*\*\*s of this invention are listed below. In addition, antibodies that specifically bind such post-translational modifications may be useful as a diagnostic or as therapeutic. The PTMs and other motifs were predicted by using the ProSite Dictionary of Proteins Sites and Patterns (Bairoch *et al.*, *Nucleic Acids Res.* 25(1):217-221 (1997)), the following motifs, including PTMs, were predicted for the \*\*\*XSP\*\*\*s of the invention. The signal peptides were detected by using the SignalP 2.0, see Nielsen *et al.*, *Protein Engineering* 12, 3-9 (1999). Prediction of transmembrane helices in proteins was performed by the application TMHMM 2.0, "currently the best performing transmembrane prediction program", according to authors (Krogh *et al.*, *Journal of Molecular Biology*, 305(3):567-580, (2001); Moller *et al.*, *Bioinformatics*, 17(7):646-653, (2001); Sonnhammer, *et al.*, *A hidden Markov model for predicting transmembrane helices in protein sequences* in Glasgow, *et al.* Ed. Proceedings of the Sixth International Conference on Intelligent Systems for Molecular Biology, pages 175-182, Menlo Park, CA, 1998. AAAI Press. The PSORT II program may also be used to predict cellular localizations. Horton *et al.*, *Intelligent Systems for Molecular Biology* 5: 147-152 (1997).
- The table below includes the following sequence annotations: Signal peptide presence; TM (number of membrane domain, topology in orientation and position); Amino acid location and antigenic index (location, AI score, length); PTM and other motifs (type, amino acid residue locations); and functional domains.

AA SEQ ID	Sig P	TMHMM	Antigenicity	PTM	Domain
DEX0432_005.aa .1			160-170, 1.17, 11; 96- 113, 1.09, 18	Amidation 3-6; Camp_Phospho_Site 133-136; Glycosaminoglycan 71-74; Myristyl 60-65;61-66;70- 75;72-77;113- 118;115-120; Pkc_Phospho_Site 3-5;47-49;132- 134;140-142;	
DEX0432_010.aa .1				Asn_Glycosylation 3-6; Myristyl 8- 13;	
DEX0432_013.aa			404-414, 1.14, 11;	Amidation 352- 355;	

.1			312-324, 1.02, 13; 466-476, 1.00, 11	Asn_Glycosylation 609-612; Camp_Phospho_Site 216-219;355-358; Ck2_Phospho_Site 80-83;156- 159;298-301;330- 333;399-402;403- 406;416-419;429- 432;537-540;551- 554;596-599; Glycosaminoglycan 417-420; Myristyl 43-48;85-90;370- 375;374-379;412- 417;424-429;492- 497; Pkc_Phospho_Site 9-11;58-60;143- 145;268-270;298- 300;409-411;471- 473;481-483;482- 484;510-512; Protein_Kinase_At p 68-91; Protein_Kinase_St 181-193;	
DEX0432 _015.aa .1				Asn_Glycosylation 13-16; Ck2_Phospho_Site 15-18; Myristyl 36-41;85-90; Pkc_Phospho_Site 73-75;89-91; Tyr_Phospho_Site 80-87;81-87;	
DEX0432 _016.aa .1		1 i21- 430		Amidation 76-79; Asn_Glycosylation 7-10;136-139; Ck2_Phospho_Site 138-141; Myristyl 111-116;159- 164;206-211; Pkc_Phospho_Site 47-49;61-63;97- 99;194-196;210- 212; Ribosomal_L6_2 191-212; Tyr_Phospho_Site 201-208;202-208;	
DEX0432 _017.aa .1				Asn_Glycosylation 22-25;	
DEX0432 _018.aa .1			27-49, 1.23, 23	Pkc_Phospho_Site 3-5;6-8;39-41; Ribosomal_L39e 30-46;	
DEX0432 _019.aa		1 i28-			

.1		500			
DEX0432 _021.aa .1		1 i96- 1180		Myristyl 57-62; Pkc_Phospho_Site 4-6;	
DEX0432 _023.aa .1			79-94, 1.06, 16	Amidation 10- 13;79-82; Asn_Glycosylation 104-107; Myristyl 19-24;66-71;76- 81;87-92; Pkc_Phospho_Site 34-36; Tyr_Phospho_Site 93-100;	
DEX0432 _025.aa .1			23-34, 1.04, 12	Camp_Phospho_Site 64-67; Ck2_Phospho_Site 5-8; Myristyl 54- 59;72-77;76-81; Pkc_Phospho_Site 5-7;30-32;50- 52;55-57;	
DEX0432 _026.aa .1				Ck2_Phospho_Site 65-68;90-93;129- 132; Myristyl 72- 77;106-111;126- 131; Pkc_Phospho_Site 19-21;89-91;	
DEX0432 _031.aa .1		3 i13- 35045 - 67i13 3- 1550	155-168, 1.24, 14, 79- 95, 1.09, 17	Asn_Glycosylation 81-84;105-108; Ck2_Phospho_Site 145-148; Myristyl 4-9;15-20;31- 36;141-146;151- 156; Pkc_Phospho_Site 10-12;85-87;155- 157; Prokar_Lipoprotei n 52-62;54-64;	
DEX0432 _033.aa .1			15-29, 1.14, 15	Asn_Glycosylation 11-14; Ck2_Phospho_Site 23-26;51-54; Myristyl 48-53;	
DEX0432 _035.aa .1			56-116, 1.03, 61	Ck2_Phospho_Site 43-46;55-58;92- 95;97-100; Myristyl 62- 67;105-110;108- 113; Pkc_Phospho_Site 40-42;43-45;94- 96;	
DEX0432 _036.aa .2	Y	1 - 01160 - 1182i	1154- 1189,1.349; 1097- 1107,1.225;	Atpase_Alpha_Beta 959-968; Asn_Glycosylation 963-966, 981-984;	PS00152, SEA, SEA, PRO_RICH, SEA,

			6-24, 1.22; 1132- 1152, 1.158; 98-111, 1.149; 889- 901, 1.134; 1034- 1053, 1.133; 949-962, 1.12; 56-65, 1.12; 1017- 1029, 1.112; 970- 977, 1.105; 909- 922, 1.096; 77-85, 1.092; 369- 381, 1.088; 569- 581, 1.088; 509- 521, 1.088; 429- 441, 1.088; 449- 461, 1.088; 669- 681, 1.088; 389- 401, 1.088; 609- 621, 1.088; 349- 361, 1.088; 469- 481, 1.088; 249- 261, 1.088; 129- 141, 1.088; 709- 721, 1.088; 329- 341, 1.088; 209- 221, 1.088; 489- 501, 1.088; 269- 281, 1.088; 409- 421, 1.088; 829- 841, 1.088; 649- 661, 1.088; 189- 201, 1.088; 769-	Ck2_Phospho_Site 52-55, 125-128, 145-148, 165-168, 185-188, 205-208, 225-228, 245-248, 265-268, 285-288, 305-308, 325-328, 345-348, 365-368, 385-388, 405-408, 425-428, 445-448, 465-468, 485-488, 505-508, 525-528, 545-548, 565-568, 585-588, 605-608, 625-628, 645-648, 665-668, 685-688, 705-708, 725-728, 745-748, 765-768, 785-788, 805-808, 825-828, 845-848, 865-868, 885-888, 905-908, 926-929, 946-949; Glycosaminoglycan 911-914; Myristyl 28-33, 72-77, 74- 79, 80-85, 94-99, 100-105, 969-974, 973-978; Pkc_Phospho_Site 45-47, 54-56, 984-986;	
--	--	--	---	---	--

			781, 1.088; 849- 861, 1.088; 589- 601, 1.088; 869- 881, 1.088; 930- 942, 1.088; 529- 541, 1.088; 789- 801, 1.088; 729- 741, 1.088; 309- 321, 1.088; 289- 301, 1.088; 809- 821, 1.088; 549- 561, 1.088; 229- 241, 1.088; 149- 161, 1.088; 629- 641, 1.088; 749- 761, 1.088; 689- 701, 1.088; 169- 181, 1.088; 1076- 1085, 1.088; 1216- 1223, 1.086; 1113- 1119, 1.082; 1241- 1253, 1.08; 989- 1000, 1.077; 115- 121, 1.065; 1087- 1093, 1.058; 42-48, 1.058; 1067- 1073, 1.047		
DEX0432 _036.aa .3	Y	1 - 0551 - 573i	545- 580, 1.349; 426- 450, 1.225; 522- 543, 1.224; 6 - 24, 1.22; 583 - 607, 1.195;	Atpase_Alpha_Beta 219-228; Amidation 718 - 721; Asn_Glycosylation 223-226, 241-244, 295-298, 321-324, 482-485;	PS00152, PRO_RICH, SEA,

			352- 409, 1.172; 488- 513, 1.156; 98-111, 1.149; 294- 313, 1.133; 209-222, 1.12; 56-65, 1.12; 277- 289, 1.112; 336- 350, 1.111; 230- 237, 1.105; 648- 656, 1.102; 666- 676, 1.102; 77-85, 1.092; 170- 182, 1.088; 190- 202, 1.088; 149- 162, 1.088; 129- 141, 1.088; 634- 641, 1.086; 475- 484, 1.083; 456- 462, 1.082; 249- 260, 1.077; 115- 121, 1.065; 42-48, 1.058; 327-333, 1.047	Ck2_Phospho_Site 52-55, 125-128, 145-148, 166-169, 186-189, 206-209, 276-279, 322-325, 323-326, 351-354, 484-487, 646-649, 651-654; Glycosaminoglycan 520-523, 549-552; Myristyl 28-33, 72-77, 74-79, 80- 85, 94-99, 100- 105, 229-234, 233-238, 383-388, 394-399, 416-421, 519-524, 523-528, 593-598, 711-716, 715-720, 726-731; Pkc_Phospho_Site 45-47, 54-56, 244-246, 275-277, 417-419, 520-522, 526-528, 648-650, 730-732;	
DEX0432 _036.aa .4	y	1 - o428- 450i	422- 457, 1.349; 365- 375, 1.225; 6- 21, 1.22; 400- 420, 1.158; 107- 120, 1.149; 302- 321, 1.133; 217-230, 1.12; 65-74, 1.12; 285- 297, 1.112; 26-33, 1.111; 238- 245, 1.105; 86-94, 1.092; 198- 210, 1.088;	Atpase_Alpha_Beta 227-236; Asn_Glycosylation 231-234, 249-252, 303-306, 329-332, 407-410; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 194-197, 214-217, 284-287, 330-333, 331-334, 409-412, 414-417, 496-499, 501-504; Glycosaminoglycan 426-429; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 237-242, 241-246,	PS00152, SEA, SEA, PRO_RICH, SEA,

			178- 190, 1.088; 138- 150, 1.088; 158- 170, 1.088; 344- 353, 1.088; 484- 491, 1.086; 381- 387, 1.082; 509-521, 1.08; 257- 268, 1.077; 124- 130, 1.065; 355- 361, 1.058; 51-57, 1.058; 335-341, 1.047	358-363, 509-514, 512-517; Pkc_Phospho_Site 54-56, 63-65, 252-254, 283-285, 498-500;	
DEX0432 _036.aa .5	y	1 - o419- 441i	413- 448, 1.349; 356- 366, 1.225; 6- 24, 1.22; 391- 411, 1.158; 98-111, 1.149; 293- 312, 1.133; 208-221, 1.12; 56-65, 1.12; 276- 288, 1.112; 229- 236, 1.105; 77-85, 1.092; 189- 201, 1.088; 129- 141, 1.088; 169- 181, 1.088; 149- 161, 1.088; 335- 344, 1.088; 475- 482, 1.086; 372- 378, 1.082; 500-512, 1.08; 248- 259, 1.077; 115- 121, 1.065; 346- 352, 1.058; 42-48, 1.058; 326-332, 1.047	Atpase_Alpha_Beta 218-227; Asn_Glycosylation 222-225, 240-243, 294-297, 320-323, 398-401; Ck2_Phospho_Site 52-55, 125-128, 145-148, 165-168, 185-188, 205-208, 275-278, 321-324, 322-325, 400-403, 405-408, 487-490, 492-495; Glycosaminoglycan 417-420; Myristyl 28-33, 72-77, 74- 79, 80-85, 94-99, 100-105, 228-233, 232-237, 349-354, 500-505, 503-508; Pkc_Phospho_Site 45-47, 54-56, 243-245, 274-276, 489-491;	PS00152, SEA, SEA, PRO_RICH, SEA,

DEX0432 _036.aa .6	N	O -o	72-91, 1.23; 93-106, 1.204; 53-67, 1.116; 14-25, 1.088; 33-45, 1.088; 5-12, 1.055	Amidation 74-77; Ck2_Phospho_Site 29-32, 49-52, 94- 97; Pkc_Phospho_Site 74-76, 98-100; Tyr_Phospho_Site 103-109;	
DEX0432 _036.aa .7	Y	O -o	6-21, 1.22; 151- 171, 1.182; 107- 120, 1.149; 65-74, 1.12; 26-33, 1.111; 86-94, 1.092; 143- 149, 1.071; 124- 130, 1.065; 51-57, 1.058	Ck2_Phospho_Site 61-64, 134-137; Glycosaminoglycan 153-156; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 152-157, 154-159, 169-174; Pkc_Phospho_Site 54-56, 63-65; Prokar_Lipoprotei n 149-159;	
DEX0432 _036.aa .8	Y	1 - 0379- 401i	373- 408, 1.349; 316- 326, 1.225; 6- 24, 1.22; 351- 371, 1.158; 98-111, 1.149; 253- 272, 1.133; 168-181, 1.12; 56-65, 1.12; 236- 248, 1.112; 189- 196, 1.105; 77-85, 1.092; 149- 161, 1.088; 129- 141, 1.088; 295- 304, 1.088; 435- 442, 1.086; 332- 338, 1.082; 460-472, 1.08; 208- 219, 1.077; 115- 121, 1.065; 306- 312, 1.058; 42-48, 1.058; 286-292, 1.047	Atpase_Alpha_Beta 178-187; Asn_Glycosylation 182-185, 200-203, 254-257, 280-283, 358-361; Ck2_Phospho_Site 52-55, 125-128, 145-148, 165-168, 235-238, 281-284, 282-285, 360-363, 365-368, 447-450, 452-455; Glycosaminoglycan 377-380; Myristyl 28-33, 72-77, 74- 79, 80-85, 94-99, 100-105, 188-193, 192-197, 309-314, 460-465, 463-468; Pkc_Phospho_Site 45-47, 54-56, 203-205, 234-236, 449-451;	PS00152, SEA, SEA, SEA,
DEX0432 _036.aa .10	Y	O -o	163-174, 1.22; 4-13, 1.198; 208- 218, 1.191;	Camp_Phospho_Site 189-192; Ck2_Phospho_Site 47-50, 107-110,	C2, C2, C2_DOMAIN_ 2, PR00399,

			221- 228, 1.177; 43-73, 1.167; 116- 153, 1.151; 15-28, 1.145; 31-41, 1.138; 78-90, 1.109; 92-101, 1.101; 198-205, 1.07; 188-194, 1.046	114-117, 116-119, 133-136, 161-164, 218-221; Myristyl 45-50, 66-71; Pkc_Phospho_Site 42-44, 143-145, 192-194; Tyr_Phospho_Site 96-103, 194-201;	
DEX0432 _036.aa .11	N	0 -o	25-55, 1.167; 60-96, 1.161; 13-23, 1.138; 4-10, 1.107; 98-104, 1.056	Ck2_Phospho_Site 29-32; Myristyl 27-32, 48-53, 101-106; Pkc_Phospho_Site 24-26;	
DEX0432 _036.aa .12	Y	1 - 0388- 410i	382- 417, 1.349; 325- 335, 1.225; 6- 21, 1.22; 360- 380, 1.158; 107- 120, 1.149; 262- 281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 198- 205, 1.105; 86-94, 1.092; 158- 170, 1.088; 138- 150, 1.088; 304- 313, 1.088; 444- 451, 1.086; 341- 347, 1.082; 469-481, 1.08; 217- 228, 1.077; 124- 130, 1.065; 315- 321, 1.058; 51-57, 1.058; 295-301, 1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292, 367-370; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 369-372, 374-377, 456-459, 461-464; Glycosaminoglycan 386-389; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 318-323, 469-474, 472-477; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245, 458-460;	PS00152, SEA, SEA, SEA,
DEX0432 _036.aa .13	Y	1 - 0367- 389i	361- 396, 1.349; 304- 314, 1.225; 6- 20, 1.22; 339- 359, 1.158;	Atpase_Alpha_Beta 166-175; Asn_Glycosylation 170-173, 188-191, 242-245, 268-271, 346-349;	PS00152, SEA, SEA, SEA,

			86-99, 1.149; 241- 260, 1.133; 156-169, 1.12; 44-53, 1.12; 224- 236, 1.112; 177- 184, 1.105; 65-73, 1.092; 137- 149, 1.088; 117- 129, 1.088; 283- 292, 1.088; 423- 430, 1.086; 320- 326, 1.082; 448-460, 1.08; 196- 207, 1.077; 103- 109, 1.065; 294- 300, 1.058; 30-36, 1.058; 274-280, 1.047	Ck2_Phospho_Site 24-27, 40-43, 113-116, 133-136, 153-156, 223-226, 269-272, 270-273, 348-351, 353-356, 435-438, 440-443; Glycosaminoglycan 365-368; Myristyl 60-65, 62-67, 68- 73, 82-87, 88-93, 176-181, 180-185, 297-302, 448-453, 451-456; Pkc_Phospho_Site 33-35, 42-44, 191-193, 222-224, 437-439;	
DEX0432 _036.aa .14	N	1 - 0428- 450i	422- 457, 1.349; 19-52, 1.265; 365- 375, 1.225; 400- 420, 1.158; 147- 160, 1.149; 302- 321, 1.133; 217-230, 1.12; 105-114, 1.12; 63-73, 1.114; 285- 297, 1.112; 238- 245, 1.105; 126- 134, 1.092; 198- 210, 1.088; 178- 190, 1.088; 344- 353, 1.088; 484- 491, 1.086; 381- 387, 1.082; 509-521, 1.08;	Atpase_Alpha_Beta 227-236; Asn_Glycosylation 231-234, 249-252, 303-306, 329-332, 407-410; Ck2_Phospho_Site 101-104, 174-177, 194-197, 214-217, 284-287, 330-333, 331-334, 409-412, 414-417, 496-499, 501-504; Glycosaminoglycan 426-429; Myristyl 22-27, 77-82, 121-126, 123-128, 129-134, 143-148, 149-154, 237-242, 241-246, 358-363, 509-514, 512-517; Pkc_Phospho_Site 94-96, 103-105, 252-254, 283-285, 498-500;	PS00152, SEA, SEA, SEA,

			257- 268, 1.077; 164- 170, 1.065; 355- 361, 1.058; 91-97, 1.058; 335-341, 1.047		
DEX0432 _036.aa .15	Y	1 - 0339- 361i	333- 368, 1.349; 276- 286, 1.225; 6- 24, 1.22; 311- 331, 1.158; 98-111, 1.149; 213- 232, 1.133; 128-141, 1.12; 56-65, 1.12; 196- 208, 1.112; 149- 156, 1.105; 77-85, 1.092; 255- 264, 1.088; 395- 402, 1.086; 292- 298, 1.082; 420-432, 1.08; 168- 179, 1.077; 115- 121, 1.065; 266- 272, 1.058; 42-48, 1.058; 246-252, 1.047	Atpase_Alpha_Beta 138-147; Asn_Glycosylation 142-145, 160-163, 214-217, 240-243, 318-321; Ck2_Phospho_Site 52-55, 125-128, 195-198, 241-244, 242-245, 320-323, 325-328, 407-410, 412-415; Glycosaminoglycan 337-340; Myristyl 28-33, 72-77, 74- 79, 80-85, 94-99, 100-105, 148-153, 152-157, 269-274, 420-425, 423-428; Pkc_Phospho_Site 45-47, 54-56, 163-165, 194-196, 409-411;	PS00152, SEA, SEA, SEA,
DEX0432 _036.aa .16	Y	2 - i7- 29017 7- 199i	171- 206, 1.349; 114- 124, 1.225; 6- 24, 1.22; 149- 169, 1.158; 55-70, 1.133; 93-102, 1.088; 233- 240, 1.086; 130- 136, 1.082; 258-270, 1.08; 104- 110, 1.058; 42-48, 1.058; 84-90, 1.047	Asn_Glycosylation 78-81, 156-159; Ck2_Phospho_Site 52-55, 79-82, 80- 83, 158-161, 163- 166, 245-248, 250-253; Glycosaminoglycan 175-178; Myristyl 28-33, 107-112, 258-263, 261-266; Pkc_Phospho_Site 45-47, 54-56, 247-249;	SEA, SEA, SEA,
DEX0432 _036.aa .17	Y	0 - o	6-21, 1.22; 326- 344, 1.216; 107-	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212,	PS00152, SEA, SEA, SEA,

			120,1.149; 262- 281,1.133; 177-190,1.12; 65-74,1.12; 23-33,1.114; 245- 257,1.112; 198- 205,1.105; 86-94,1.092; 158- 170,1.088; 138- 150,1.088; 304- 313,1.088; 217- 228,1.077; 124- 130,1.065; 315- 321,1.058; 51-57,1.058; 295-301,1.047	263-266, 289-292; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294; Glycosaminoglycan 332-335; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 318-323, 333-338; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245;	
DEX0432 _036.aa .19	Y	0 -o	6-21,1.22; 107- 120,1.149; 262- 281,1.133; 177-190,1.12; 65-74,1.12; 23-33,1.114; 245- 257,1.112; 304- 313,1.111; 198- 205,1.105; 86-94,1.092; 138- 150,1.088; 158- 170,1.088; 217- 228,1.077; 124- 130,1.065; 51-57,1.058; 295-301,1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245;	PS00152, SEA,
DEX0432 _036.aa .20	Y	2 - i7- 29o13 4- 156i	128- 163,1.349; 69-81,1.225; 6-24,1.22; 106- 126,1.158; 190- 197,1.086; 87-93,1.082; 215-227,1.08;	Asn_Glycosylation 113-116; Ck2_Phospho_Site 52-55, 67-70, 115-118, 120-123, 202-205, 207-210; Glycosaminoglycan 132-135; Myristyl 28-33, 215-220, 218-223;	SEA,

			42-48, 1.058	Pkc_Phospho_Site 45-47, 54-56, 64- 66, 67-69, 204- 206;	
DEX0432 _036.aa .21	Y	1 - 0518- 540i	512- 547, 1.349; 409- 431, 1.227; 325- 335, 1.225; 6- 21, 1.22; 360- 374, 1.186; 107- 120, 1.149; 262- 281, 1.133; 456- 475, 1.133; 497- 510, 1.123; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 438- 451, 1.112; 245- 257, 1.112; 198- 205, 1.105; 86-94, 1.092; 138- 150, 1.088; 158- 170, 1.088; 304- 313, 1.088; 574- 581, 1.086; 341- 347, 1.082; 599-611, 1.08; 217- 228, 1.077; 124- 130, 1.065; 381- 392, 1.058; 315- 321, 1.058; 51-57, 1.058; 489- 495, 1.047; 295-301, 1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292, 367-370, 457-460, 483-486; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 369-372, 434-437, 484-487, 485-488, 586-589, 591-594; Glycosaminoglycan 516-519; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 318-323, 393-398, 397-402, 403-408, 412-417, 422-427, 599-604, 602-607; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245, 588-590;	PS00152, SEA, SEA, SEA,
DEX0432 _036.aa .22	Y	0 -o	316- 342, 1.228; 6- 21, 1.22; 107- 120, 1.149; 344- 369, 1.148; 262-	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292; Ck2_Phospho_Site 61-64, 134-137,	PS00152, PS00261, SEA,

			281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 198- 205, 1.105; 86-94, 1.092; 138- 150, 1.088; 158- 170, 1.088; 217- 228, 1.077; 124- 130, 1.065; 51-57, 1.058; 295-301, 1.047	154-157, 174-177, 244-247, 290-293, 291-294; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 312-317, 321-326, 323-328; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245; Glyco_Hormone_Bet a_1 328-334;	
DEX0432 _036.aa .23	y	0 -o	6-24, 1.22; 98-111, 1.149; 213- 232, 1.133; 128-141, 1.12; 56-65, 1.12; 196- 208, 1.112; 149- 156, 1.105; 77-85, 1.092; 168- 179, 1.077; 115- 121, 1.065; 42-48, 1.058; 246-252, 1.047	Atpase_Alpha_Beta 138-147; Asn_Glycosylation 142-145, 160-163, 214-217, 240-243; Ck2_Phospho_Site 52-55, 125-128, 195-198, 241-244, 242-245; Myristyl 28-33, 72-77, 74- 79, 80-85, 94-99, 100-105, 148-153, 152-157; Pkc_Phospho_Site 45-47, 54-56, 163-165, 194-196;	PS00152, SEA,
DEX0432 _036.aa .24	y	1 - o388- 410i	382- 417, 1.349; 325- 335, 1.225; 6- 21, 1.22; 360- 380, 1.158; 107- 120, 1.149; 262- 281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 198- 205, 1.105; 86-94, 1.092; 158- 170, 1.088; 138- 150, 1.088; 304- 313, 1.088;	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292, 367-370; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 369-372, 374-377, 456-459, 461-464; Glycosaminoglycan 386-389; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 318-323, 487-492; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245, 458-460, 488-490,	PS00152, SEA, SEA, SEA,

			444- 451, 1.086; 341- 347, 1.082; 217- 228, 1.077; 458- 464, 1.073; 124- 130, 1.065; 315- 321, 1.058; 51-57, 1.058; 295-301, 1.047	491-493;	
DEX0432 _036.aa .25	y	1 - o388- 410i	382- 417, 1.349; 325- 335, 1.225; 6- 21, 1.22; 360- 380, 1.158; 107- 120, 1.149; 262- 281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 447- 454, 1.106; 198- 205, 1.105; 86-94, 1.092; 138- 150, 1.088; 158- 170, 1.088; 304- 313, 1.088; 341- 347, 1.082; 217- 228, 1.077; 124- 130, 1.065; 315- 321, 1.058; 51-57, 1.058; 295-301, 1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292, 367-370; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 369-372, 374-377; Glycosaminoglycan 386-389; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 318-323; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245, 459-461;	PS00152, SEA, SEA, NLS_BP, SEA,
DEX0432 _036.aa .26	y	0 -o	6-24, 1.22; 75-83, 1.147; 110- 117, 1.086; 135-147, 1.08; 42-48, 1.058; 66-72, 1.047	Asn_Glycosylation 60-63; Ck2_Phospho_Site 52-55, 61-64, 62- 65, 122-125, 127- 130; Myristyl 28-33, 135-140, 138-143; Pkc_Phospho_Site 45-47, 54-56,	SEA,

				124-126;	
DEX0432 _036.aa .27	Y	O -o	6-24,1.22; 93-101,1.147; 55-70,1.133; 128- 135,1.086; 153-165,1.08; 42-48,1.058; 84-90,1.047	Asn_Glycosylation 78-81; Ck2_Phospho_Site 52-55, 79-82, 80- 83, 140-143, 145- 148; Myristyl 28-33, 153-158, 156-161; Pkc_Phospho_Site 45-47, 54-56, 142-144;	SEA,
DEX0432 _036.aa .28	N	O -o	4-10,1.093; 39-46,1.086; 64-76,1.08	Ck2_Phospho_Site 51-54, 56-59; Myristyl 64-69, 67-72; Pkc_Phospho_Site 53-55;	
DEX0432 _036.aa .29	Y	O -o	325- 335,1.225; 6- 21,1.22; 107- 120,1.149; 262- 281,1.133; 360- 377,1.124; 177-190,1.12; 65-74,1.12; 23-33,1.114; 245- 257,1.112; 198- 205,1.105; 86-94,1.092; 138- 150,1.088; 158- 170,1.088; 304- 313,1.088; 341- 347,1.082; 217- 228,1.077; 124- 130,1.065; 315- 321,1.058; 51-57,1.058; 295-301,1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292, 367-370; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 369-372; Myristyl 37-42, 81-86, 83-88, 89- 94, 103-108, 109- 114, 197-202, 201-206, 318-323; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245;	PS00152, SEA, SEA, SEA,
DEX0432 _036.aa .30	Y	O -o	4-16,1.196; 20-26,1.11	Ck2_Phospho_Site 33-36; Myristyl 22-27;	
DEX0432 _036.aa .31	Y	1 - 0168- 190i	162- 197,1.349; 105- 115,1.225; 6- 21,1.22; 140- 160,1.158; 23-33,1.114;	Asn_Glycosylation 69-72, 147-150; Ck2_Phospho_Site 61-64, 70-73, 71- 74, 149-152, 154- 157, 236-239, 241-244;	SEA, SEA, SEA,

			84-93, 1.088; 224- 231, 1.086; 121- 127, 1.082; 249-261, 1.08; 95-101, 1.058; 51-57, 1.058; 75-81, 1.047	Glycosaminoglycan 166-169; Myristyl 37-42, 98-103, 249-254, 252-257; Pkc_Phospho_Site 54-56, 63-65, 238-240;	
DEX0432 _036.aa .32	Y	1 - 0145- 167i	139- 174, 1.349; 82-92, 1.225; 6-21, 1.22; 117- 137, 1.158; 23-33, 1.114; 63-70, 1.095; 201- 208, 1.086; 98-104, 1.082; 226-238, 1.08; 72-78, 1.058; 51-57, 1.058	Asn_Glycosylation 124-127; Ck2_Phospho_Site 61-64, 126-129, 131-134, 213-216, 218-221; Glycosaminoglycan 143-146; Myristyl 37-42, 75-80, 226-231, 229-234; Pkc_Phospho_Site 54-56, 63-65, 215-217;	SEA, SEA, SEA,
DEX0432 _036.aa .33	N	0 -o	4-17, 1.195; 44-51, 1.086; 58-64, 1.073	Ck2_Phospho_Site 56-59, 61-64; Myristyl 87-92; Pkc_Phospho_Site 58-60, 88-90, 91- 93;	
DEX0432 _036.aa .34	N	1 - 0324- 346i	318- 353, 1.349; 261- 271, 1.225; 296- 316, 1.158; 43-56, 1.149; 198- 217, 1.133; 113-126, 1.12; 4-10, 1.12; 181- 193, 1.112; 134- 141, 1.105; 22-30, 1.092; 74-86, 1.088; 94-106, 1.088; 240- 249, 1.088; 380- 387, 1.086; 277- 283, 1.082; 405-417, 1.08; 153- 164, 1.077; 60-66, 1.065; 251- 257, 1.058; 231-237, 1.047	Atpase_Alpha_Beta 123-132; Asn_Glycosylation 127-130, 145-148, 199-202, 225-228, 303-306; Ck2_Phospho_Site 70-73, 90-93, 110-113, 180-183, 226-229, 227-230, 305-308, 310-313, 392-395, 397-400; Glycosaminoglycan 322-325; Myristyl 17-22, 19-24, 25- 30, 39-44, 45-50, 133-138, 137-142, 254-259, 405-410, 408-413; Pkc_Phospho_Site 148-150, 179-181, 394-396;	PS00152, SEA, SEA, SEA,

DEX0432 _036.aa .35	Y	1 - o389- 411i	383- 418,1.349; 326- 336,1.225; 7- 22,1.22; 361- 381,1.158; 108- 121,1.149; 263- 282,1.133; 178-191,1.12; 66-75,1.12; 24-34,1.114; 246- 258,1.112; 199- 206,1.105; 87-95,1.092; 159- 171,1.088; 139- 151,1.088; 305- 314,1.088; 445- 452,1.086; 342- 348,1.082; 470-482,1.08; 218- 229,1.077; 125- 131,1.065; 316- 322,1.058; 52-58,1.058; 296-302,1.047	Atpase_Alpha_Beta 188-197; Asn_Glycosylation 192-195, 210-213, 264-267, 290-293, 368-371; Ck2_Phospho_Site 62-65, 135-138, 155-158, 175-178, 245-248, 291-294, 292-295, 370-373, 375-378, 457-460, 462-465; Glycosaminoglycan 387-390; Myristyl 38-43, 82-87, 84- 89, 90-95, 104- 109, 110-115, 198-203, 202-207, 319-324, 470-475, 473-478; Pkc_Phospho_Site 55-57, 64-66, 213-215, 244-246, 459-461;	PS00152, SEA, SEA, SEA,
DEX0432 _036.aa .36	Y	2 - i7- 29015 9- 181i	153- 188,1.349; 96-106,1.225; 6-24,1.22; 131- 151,1.158; 75-84,1.088; 215- 222,1.086; 112- 118,1.082; 240-252,1.08; 86-92,1.058; 42-48,1.058; 66-72,1.047	Asn_Glycosylation 60-63, 138-141; Ck2_Phospho_Site 52-55, 61-64, 62- 65, 140-143, 145- 148, 227-230, 232-235; Glycosaminoglycan 157-160; Myristyl 28-33, 89-94, 240-245, 243-248; Pkc_Phospho_Site 45-47, 54-56, 229-231;	SEA, SEA, SEA,
DEX0432 _036.aa .37	Y	1 - o421- 443i	415- 450,1.349; 358- 368,1.225; 6- 21,1.22; 320- 346,1.163; 393- 413,1.158;	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292, 400-403; Ck2_Phospho_Site 61-64, 134-137,	PS00152, SEA, SEA, SEA,

			107- 120, 1.149; 262- 281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 304- 318, 1.111; 198- 205, 1.105; 86-94, 1.092; 138- 150, 1.088; 158- 170, 1.088; 477- 484, 1.086; 374- 380, 1.082; 502-514, 1.08; 217- 228, 1.077; 124- 130, 1.065; 348- 354, 1.058; 51-57, 1.058; 295-301, 1.047	154-157, 174-177, 244-247, 290-293, 291-294, 319-322, 402-405, 407-410, 489-492, 494-497; Glycosaminoglycan 419-422; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 351-356, 502-507, 505-510; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245, 491-493;	
DEX0432 _036.aa .38	N	1 - 084- 106i	78-113, 1.349; 21-31, 1.225; 56-76, 1.158; 140- 147, 1.086; 37-43, 1.082; 165-177, 1.08; 11-17, 1.058	Asn_Glycosylation 63-66; Ck2_Phospho_Site 65-68, 70-73, 152-155, 157-160; Glycosaminoglycan 82-85; Myristyl 14-19, 165-170, 168-173; Pkc_Phospho_Site 154-156;	SEA, SEA, SEA,
DEX0432 _036.aa .39	Y	2 - i7- 29013 6- 158i	130- 165, 1.349; 73-83, 1.225; 6-24, 1.22; 108- 128, 1.158; 54-61, 1.095; 192- 199, 1.086; 89-95, 1.082; 217-229, 1.08; 63-69, 1.058; 42-48, 1.058	Asn_Glycosylation 115-118; Ck2_Phospho_Site 52-55, 117-120, 122-125, 204-207, 209-212; Glycosaminoglycan 134-137; Myristyl 28-33, 66-71, 217-222, 220-225; Pkc_Phospho_Site 45-47, 54-56, 206-208;	SEA, SEA, SEA,
DEX0432 _036.aa .41	Y	0 -o	325- 335, 1.225; 6- 21, 1.22; 373- 393, 1.155; 107-	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292,	PS00152, SEA, SEA, SEA,

			120,1.149; 262- 281,1.133; 177-190,1.12; 65-74,1.12; 23-33,1.114; 245- 257,1.112; 198- 205,1.105; 86-94,1.092; 158- 170,1.088; 138- 150,1.088; 304- 313,1.088; 360- 369,1.083; 341- 347,1.082; 217- 228,1.077; 124- 130,1.065; 315- 321,1.058; 51-57,1.058; 295-301,1.047	367-370; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 369-372; Myristyl 37-42, 81-86, 83-88, 89- 94, 103-108, 109- 114, 197-202, 201-206, 318-323; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245;	
DEX0432 _036.aa .42	Y	0 -o	6-21,1.22; 107- 120,1.149; 262- 281,1.133; 177-190,1.12; 65-74,1.12; 23-33,1.114; 245- 257,1.112; 198- 205,1.105; 86-94,1.092; 138- 150,1.088; 158- 170,1.088; 304- 313,1.088; 217- 228,1.077; 124- 130,1.065; 315- 321,1.058; 51-57,1.058; 295-301,1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 318-323; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245;	PS00152, SEA,
DEX0432 _036.aa .43	Y	0 -o	325- 335,1.225; 6- 21,1.22; 360- 379,1.189;	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212,	PS00152, SEA, SEA, SEA,

			107- 120, 1.149; 381- 406, 1.148; 262- 281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 198- 205, 1.105; 86-94, 1.092; 138- 150, 1.088; 158- 170, 1.088; 304- 313, 1.088; 341- 347, 1.082; 217- 228, 1.077; 124- 130, 1.065; 315- 321, 1.058; 51-57, 1.058; 295-301, 1.047	263-266, 289-292, 367-370; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 369-372; Myristyl 37-42, 81-86, 83-88, 89- 94, 103-108, 109- 114, 197-202, 201-206, 318-323; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245;	
DEX0432 _036.aa .44	Y	0 -o	6-21, 1.22; 107- 120, 1.149; 304- 312, 1.147; 262- 281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 198- 205, 1.105; 86-94, 1.092; 138- 150, 1.088; 158- 170, 1.088; 339- 346, 1.086; 364-376, 1.08; 217- 228, 1.077; 124- 130, 1.065; 51-57, 1.058; 295-301, 1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294, 351-354, 356-359; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 364-369, 367-372; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245, 353-355;	PS00152, SEA,
DEX0432 _036.aa	Y	1 - o15-	8-43, 1.349; 70-77, 1.086;	Ck2_Phospho_Site 82-85, 87-90;	

.45		37i	95-107, 1.08	Myristyl 95-100, 98-103; Pkc_Phospho_Site 84-86;	
DEX0432 _036.aa .46	Y	0 -o	6-24, 1.22; 53-60, 1.175; 87-94, 1.086; 112-124, 1.08; 42-48, 1.058	Ck2_Phospho_Site 52-55, 99-102, 104-107; Myristyl 28-33, 112-117, 115-120; Pkc_Phospho_Site 45-47, 54-56, 101-103;	
DEX0432 _036.aa .48	Y	0 -o	6-21, 1.22; 107- 120, 1.149; 262- 281, 1.133; 177-190, 1.12; 65-74, 1.12; 23-33, 1.114; 245- 257, 1.112; 198- 205, 1.105; 86-94, 1.092; 138- 150, 1.088; 158- 170, 1.088; 304- 313, 1.088; 217- 228, 1.077; 124- 130, 1.065; 315- 321, 1.058; 51-57, 1.058; 295-301, 1.047	Atpase_Alpha_Beta 187-196; Asn_Glycosylation 191-194, 209-212, 263-266, 289-292; Camp_Phospho_Site 337-340; Ck2_Phospho_Site 61-64, 134-137, 154-157, 174-177, 244-247, 290-293, 291-294; Myristyl 37-42, 81-86, 83- 88, 89-94, 103- 108, 109-114, 197-202, 201-206, 318-323; Pkc_Phospho_Site 54-56, 63-65, 212-214, 243-245;	PS00152, SEA,
DEX0432 _039.aa .1				Myristyl 25-30;	
DEX0432 _041.aa .1				Ck2_Phospho_Site 79-82; Myristyl 35-40; 39-44; 61- 66;	
DEX0432 _045.aa .1				Asn_Glycosylation 45-48; Glycosaminoglycan 35-38; Myristyl 29-34;	

Using the PSORT II program, the following cellular localizations and the k nearest neighbors classifier values were determined (Paul Horton and Kenta Nakai, Better Prediction of Protein Cellular Localization Sites with the k Nearest Neighbors Classifier,

DEX ID NO	Localization	K value
DEX0432_5.aa.1	nuc	(k=23)
DEX0432_10.aa.1	nuc	(k=23)
DEX0432_12.aa.1	cyt	(k=23)
DEX0432_13.aa.1	nuc	(k=23)
DEX0432_15.aa.1	nuc	(k=23)
DEX0432_16.aa.1	pla	(k=23)
DEX0432_17.aa.1	cyt	(k=23)
DEX0432_18.aa.1	nuc	(k=23)
DEX0432_19.aa.1	nuc	(k=23)
DEX0432_21.aa.1	cyt	(k=23)
DEX0432_23.aa.1	cyt	(k=23)
DEX0432_25.aa.1	cyt	(k=23)
DEX0432_26.aa.1	ves	(k=9)
DEX0432_31.aa.1	pla	(k=23)
DEX0432_33.aa.1	nuc	(k=23)
DEX0432_35.aa.1	nuc	(k=23)
DEX0432_39.aa.1	exc	(k=9)
DEX0432_41.aa.1	nuc	(k=23)
DEX0432_45.aa.1	nuc	(k=23)

**Example 6: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

5 RNA is isolated from individual patients or from a family of individuals that have a phenotype of interest. cDNA is then generated from these RNA samples using protocols known in the art. *See, Sambrook (2001), supra.* The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO: 1-94. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; 10 and 60-120 seconds at 70°C, using buffer solutions described in Sidransky *et al., Science* 252(5006): 706-9 (1991). *See also Sidransky *et al., Science* 278(5340): 1054-9 (1997).*

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTHERM Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products 15 analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing. PCR products is cloned into T-tailed vectors as described in Holton *et al., Nucleic Acids Res.*, 19: 1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

20 Genomic rearrangements may also be determined. Genomic clones are nick-translated with digoxigenin deoxyuridine 5' triphosphate (Boehringer Manheim), and FISH is performed as described in Johnson *et al., Methods Cell Biol.* 35: 73-99 (1991).

Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C-and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. *Id.* Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

**Example 7: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

Antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10  $\mu$ g/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described above. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced. The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide. Next, 50  $\mu$ l of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate. 75  $\mu$ l of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution are added to each well and incubated 1 hour at room temperature.

The reaction is measured by a microtiter plate reader. A standard curve is prepared, using serial dilutions of a control sample, and polypeptide concentrations are plotted on the X-axis (log scale) and fluorescence or absorbance on the Y-axis (linear scale). The concentration of the polypeptide in the sample is calculated using the standard curve.

**Example 8: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 ,  $\mu\text{g}/\text{kg}/\text{day}$  10 to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1  $\mu\text{g}/\text{kg}/\text{hour}$  to about 50 mg/kg/hour, either by 1-4 injections per day or by continuous 15 subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, 20 topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and 25 intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semipermeable polymer matrices in the form of shaped articles, e. g., films, or microcapsules. Sustained-release matrices include polylactides (U. S. Pat. No.3,773,919, EP 58,481), copolymers of 30 L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22: 547- 556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15: 167-277 (1981), and R. Langer, Chem. Tech. 12: 98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-

release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE Epstein et al., Proc. Natl. Acad. Sci. USA 82: 3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; 5 Japanese Pat. Appl. 83-118008; U. S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is 10 formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, I. e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

For example, the formulation preferably does not include oxidizing agents and 15 other compounds that are known to be deleterious to polypeptides. Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more 20 preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that 25 enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e. g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, 30 aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

5 Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e. g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

10 Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1 % (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized  
15 polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container (s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or  
20 biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

#### **Example 9: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or  
25 normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the  
30 activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in

the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided above.

**Example 10: Method of Treating Increased Levels of the Polypeptide**

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided above.

**Example 11: Method of Treatment Using Gene Therapy**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e. g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks. pMV-7 (Kirschmeier, P. T. et al., DNA, 7: 219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5'and 3'end sequences respectively as set forth in Example 1. Preferably, the 5'primer contains an EcoRI site and the 3'primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA

ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB 101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

5       The amphotropic pA317 or GP+aml2 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred  
10      to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached  
15      producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media.

If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently  
20      infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

#### **Example 12: Method of Treatment Using Gene Therapy-In Vivo**

Another aspect of the present invention is using in vivo gene therapy methods to  
25      treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide.

The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by  
30      the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO 90/11092, WO 98/11779; U. S. Patent No. 5,693,622; 5,705,151; 5,580,859; Tabata H. et al. (1997) *Cardiovasc. Res.* 35 (3): 470-479, Chao J et al. (1997) *Pharmacol. Res.* 35 (6): 517-522, Wolff J. A. (1997) *Neuromuscul. Disord.* 7 (5): 314-318,

Schwartz B. et al. (1996) Gene Ther. 3 (5): 405-411, and Tsurumi Y. et al. (1996) Circulation 94 (12): 3281-3290.

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, breast, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P. L. et al. (1995) Ann. NY Acad. Sci. 772: 126-139 and Abdallah B. et al. (1995) Biol. Cell 85 (1): 1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, breast, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are

differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

- 5 For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 µg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection.
- 10 The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to breasts or
- 15 bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle in vivo is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e. g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 µm cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for

protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice.

5 The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

#### **Example 13: Transgenic Animals**

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e. g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (I. e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., *Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver et al., *Biotechnology (NY)* 11: 1263-1270 (1993); Wright et al., *Biotechnology (NY)* 9: 830-834 (1991); and Hoppe et al., U. S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., *Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., *Cell* 56: 313-321 (1989)); electroporation of cells or embryos (Lo, 1983, *Mol Cell. Biol.* 3: 1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e. g., Ulmer et al., *Science* 259: 1745 (1993)); introducing nucleic acid constructs into 20 embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm mediated gene transfer (Lavitrano et al., *Cell* 57: 717-723 (1989). For a review of such techniques, see Gordon, "Transgenic Animals," *Intl. Rev. Cytol.* 115: 171-229 (1989).

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., *Nature* 380: 64-66 (1996); Wilmut et al., *Nature* 385: 810813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, I. e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e. g., head-to-head tandems or head-to-tail

5 tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89: 6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide

10 transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene

15 may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265: 103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

20 Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques

25 which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

30 Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in

order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### **Example 14: Knock-Out Animals**

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E. g., see Smithies et al., *Nature* 317: 230-234 (1985); Thomas & Capecchi, *Cell* 51: 503-512 (1987); Thompson et al., *Cell* 5: 313-321 (1989)). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfet cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e. g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered

not to express the polypeptides of the invention (e. g., knockouts) are administered to a patient in vivo. Such cells may be obtained from the patient (I. e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e. g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e. g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e. g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e. g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U. S. Patent No. 5,399,349; and Mulligan & Wilson, U. S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

While preferred illustrative embodiments of the present invention are described, one skilled in the art will appreciate that the present invention can be practiced by other than the described embodiments, which are presented for purposes of illustration only and not by way of limitation. The present invention is limited only by the claims that follow.

We claim:

1. An isolated nucleic acid molecule comprising:
  - (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 95-156;
  - 5 (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94;
  - (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or
  - (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b).
- 10 2. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a cDNA.
- 15 3. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is genomic DNA.
4. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is an RNA.
- 20 5. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a mammalian nucleic acid molecule.
6. The nucleic acid molecule according to claim 5, wherein the nucleic acid molecule is a 25 human nucleic acid molecule.
7. A method for determining the presence of a breast specific nucleic acid (BSNA) in a sample, comprising the steps of:
  - (a) contacting the sample with the nucleic acid molecule of SEQ ID NO: 1-94
  - 30 under conditions in which the nucleic acid molecule will selectively hybridize to a breast specific nucleic acid; and

(b) detecting hybridization of the nucleic acid molecule to a BSNA in the sample, wherein the detection of the hybridization indicates the presence of a BSNA in the sample.

5 8. A vector comprising the nucleic acid molecule of claim 1.

9. A host cell comprising the vector according to claim 8.

10. A method for producing a polypeptide encoded by the nucleic acid molecule according  
10 to claim 1, comprising the steps of:

(a) providing a host cell comprising the nucleic acid molecule operably linked to one or more expression control sequences, and

(b) incubating the host cell under conditions in which the polypeptide is produced.

15 11. A polypeptide encoded by the nucleic acid molecule according to claim 1.

12. An isolated polypeptide selected from the group consisting of:

(a) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 95-156 ; or

20 (b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94.

13. An antibody or fragment thereof that specifically binds to:

25 (a) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 95-156 ; or

(b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94.

14. A method for determining the presence of a breast specific protein in a sample, comprising the steps of:

- (a) contacting the sample with a suitable reagent under conditions in which the  
5 reagent will selectively interact with the breast specific protein comprising an  
amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 95-  
156; and
- (b) detecting the interaction of the reagent with a breast specific protein in the  
sample, wherein the detection of binding indicates the presence of a breast specific  
10 protein in the sample.

15. A method for diagnosing or monitoring the presence and metastases of breast cancer in a patient, comprising the steps of:

- (a) determining an amount of:
- (i) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 95-156;
- (ii) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94;
- (iii) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (i) or (ii);
- (iv) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (i) or (ii);
- (v) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 95-156 ; or
- (vi) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94 and;
- (b) comparing the determined amount of the nucleic acid molecule or the polypeptide in the sample of the patient to the amount of the breast specific marker in a normal control; wherein a difference in the determined amount of the nucleic acid molecule or the polypeptide in the sample compared to the amount of

the nucleic acid molecule or the polypeptide in the normal control is associated with the presence of breast cancer.

16. A kit for detecting a risk of cancer or presence of cancer in a patient, said kit  
5 comprising a means for determining the presence of:
- (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 95-156;
  - (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94;
  - 10 (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or
  - (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b); or
  - 15 (e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 95-156 ; or
  - (f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94.
- 20 17. A method of treating a patient with breast cancer, comprising the step of administering a composition consisting of:
- (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 95-156;
  - (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94;
  - 25 (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b);
  - (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b);
  - 30 (e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 95-156 ; or

- (f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-94;  
to a patient in need thereof, wherein said administration induces an immune response  
5 against the breast cancer cell expressing the nucleic acid molecule or polypeptide.

18. A vaccine comprising the polypeptide or the nucleic acid encoding the polypeptide of claim 12.

10/517696

DT12 Rec'd PCT/PTO 13 DEC 2004

PCT/US03/18934

WO 03/106648

1

SEQUENCE LISTING

<110> diaDexus, Inc.  
Salceda, Susana  
Macina, Roberto A.  
Turner, Leah R.  
Sun, Yongming  
Liu, Chenghua

<120> Compositions and Methods Relating to Breast Specific Genes and Proteins

<130> DEX-0432

<150> US 60/389,327  
<151> 2002-06-14

<160> 171

<170> PatentIn version 3.1

<210> 1  
<211> 1574  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (89)..(180)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (1466)..(1466)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (1474)..(1474)  
<223> n=a, c, g, or t

<400> 1  
ctgaagggtt atacaatatt tacacagtgg ctacaatatt cacaaaattc ttatgttctc 60  
ttatgaaaaa tatacactt tcattttgnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 120  
nnnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 180  
gtacatgtat atatttgcc tgcattatgt ttttacttg atataaatgt attttactg 240  
tgatagtc当地 agtgccctgg ggggcaggtg tgctctatgt ggttcttctt ccattggaga 300  
gctggcgtag agatctgc当地 tgttcacaag gatgttggtt tggagatgtc tgctgctagg 360  
acctggggtg tgtgactc当地 tccatatgag agggacatct ggggtggagga gtaaattcct 420  
tgctctgaa atgccactt当地 gtagctctgg acaatgaagg acaattgact caagggtgcc 480

2

tggcttctgc	tgctgctggg	aaaaaattca	gtttatagca	ttcctgcacc	tcccaaagta	540
gataacctgg	aggtcattca	gttaacaact	gtcccctgagg	actcagttt	gggggagggg	600
ttatctggga	gaagctttag	cctgttctga	gccattagga	gacattagtg	aattggagca	660
ctggagaatc	ctacaaatgg	cctatgtctc	agaagagctg	ggacctcctt	ccagctgctg	720
cagatgctga	caggccctgg	gaggctgctg	tgctctggag	aagctggagc	agctcatttc	780
ttggcctagc	ctggctgcct	cagaaagagc	agtcaaggact	tgagggaaagc	atcaaattct	840
ataccataa	actgcagttg	gaagtcaagct	ttttgaaatg	tccagcctt	gcccaattgt	900
ttcagatcat	ctcatgcctc	aggcttggc	aggtatcctg	ccctccatct	tattccagtg	960
tgttacaccc	atcaaggcag	cagagtggat	gaaggagtaa	gtctgccctt	tgccataactg	1020
aacagctgtg	gaccccgatt	ggtgagggct	ctgcatatgc	ctgtatgaag	gagatacagg	1080
tgtgtgtgca	catgccggt	tgaagaagac	acaggcatgt	gcttctcagt	tttgctaaca	1140
gtggagctc	aacggggcag	aggaggaag	gtccatgatg	ctcagccaca	tactgttagag	1200
agaggcaatt	taatgttaaa	tgacgcacca	tcctccctcc	cacccttctc	ccagtcaact	1260
ttttttcttt	ttctagaact	actaattatc	tctcaaggct	gaaaaattaa	ttgccttagg	1320
tggagaacctt	aattcctagt	atccaccaaa	cttaactccg	tatctccata	tggtgtctcc	1380
atatctactg	tgtgagctac	ttaactgacg	ccctcttctt	ccaactgaag	gatcgcccaa	1440
cgtttttgga	ttatagaatt	attatngct	gctntcttcc	tttgggactt	ttgaatttct	1500
ttggtttcgt	tttaagaag	taacccaaca	tttcctacaa	cactaaataa	aatggtactt	1560
acctttcaaa	aaga					1574

<210> 2  
 <211> 539  
 <212> DNA  
 <213> Homo sapien

<400> 2						
cgaccgttga	ctattctcta	caaaccacaa	agacattgga	acactatacc	tattattcgg	60
cgcatgagct	ggagtcctag	gcacagctct	aagcctcctt	attcgagccg	agctgggcca	120
gccaggcaac	cttcttaggt	acgaccacat	ctacaacgtt	atcgtcacag	cccatgcatt	180
tgtaataatc	ttcttcata	taataccat	cataatcgga	ggctttggca	aaaaaaaaac	240
aaaaaaaaaa	aaaaaacctg	gggaaaacac	ggggcaaacg	cggccccggg	ggcagaaatg	300
gtacccggcc	acattccac	acacattccg	acacaagagg	cgaagacacg	acaacagccg	360
accgacacaa	cagaggcacg	ggaaaggggg	acgaagagga	ggaggagaac	agacgggacg	420
gcaacaagg	acagcgaggg	acgcagacgc	ggaggagaag	gggaaaggca	gacgggaacg	480

agaaaaaagag ccgagacggg acgcggaccc cacagggggg tcgcgagaaa agacgccc 539

<210> 3  
<211> 197  
<212> DNA  
<213> Homo sapien

<400> 3  
acttttattt caatgtatac agaagctgtg atgtttgcc tttgttagtcc tgtgctttgt 60  
tactgttaatt tttttttttt ttatacaaag cacgtgacgt ggactaatgt aaggcagatg 120  
acgtgactct taagacgtgc tatattttt cagttccctct ttacctctat agaggtttta 180  
aatttagaaat aagctgt 197

<210> 4  
<211> 1634  
<212> DNA  
<213> Homo sapien

<400> 4  
aactaacttt gtggggtttt tttgtttttt tttttatttt cttaaagccg aacgagcatg 60  
tatgtggaca gaagtggAAC acttcttggg tccaaataca agaaagtctt atatcgtaa 120  
tatgtatgata acacgttcac aaatcaaaca aaaaggaatg aaggtaaaaa acatctcgat 180  
atacttaggtc catataatatt gctcaaccct ggtcaaataa ttcaaattat cttaaaaaat 240  
aaagccgcaa gaccgtattt tattcatgtc catggagtga aaacaaataa ttccactgtt 300  
gttccaactc agccaggaga gattcaaata tatacttggc agataacctga tagaactggt 360  
cctacactcac tggactttga atgcataacct tggtttact attcaactgt atctgtggct 420  
aaggaccttc acagtggact ggttaggcct ctctctgtat gccgcaaaga catcaacccc 480  
aacatagttc accgtgttct ccacttcatg atatttgatg agaatgaatc ctggtacttc 540  
gaagacagta tcaacaccta tgcttcaaaa ccaaacaaag tggacaagga aaatgataat 600  
tttcaactca gcaaccaaatt gcacgcaatt aacggaagac tgtttggaaa taaccaaggt 660  
ataacattcc atgttggga ttagtgaat tggtatctga ttggcatagg gaatgaagct 720  
gacctgcaca cagttcacct tcatggccat agcttgaat acaagaatta gggagtgtat 780  
caatctgatg tttatgacct tcctcttggg gtctatcgaa ctgtaaaaat gtatcgaaaa 840  
gatgttggaa cctggttatt ttattgccat gttttgagc acattggtgc tggaatggat 900  
agcacttaca ctgtacttga aagaaaaggg ctgatggagc agaacctctg aagcagacaa 960  
aggagagtca gcatgaacag tttctcagaa tcttctctca atatcaggac tacatttgc 1020  
aacaaaaacca aaaactgatt agccaccgat ataatttttta cctacaacat cctattaatg 1080  
tcaataatat cattattgat acaattctaa taatcactac ccttattcct atcagtgttc 1140

atgtacattc ttagtaaaag agactttggc gcgctgtcca taaaataaat ccccccattgc 1200  
taacattctt tctttggaaa agtagatttt gcatttcaaa gaatataaaag tcaaattgga 1260  
ttggattttac aggtcatctg ttccccacaga agggtgatat tgatgttgct attgataagt 1320  
aaactttttg tggcaaaaagt gatggtagtt attttaagga tggcccaag actaaataaa 1380  
attttgtatt tatttcctaa atgtatgtaa tcattttgc ttagtatttt aacttagaac 1440  
tgcatgctat tatataatat tacctatTTt tggaaacttcc ttttctacag cataaaatatt 1500  
tgatatgata tgaatattga caagcttaca agccaaggta aagctgccaa agaaggaaaa 1560  
ctccaggggac caaggagtct gggaggaacc agctaaagac tttcatgaca atgtaccagg 1620  
gagactagtt tgag 1634

<210> 5  
<211> 891  
<212> DNA  
<213> Homo sapien

<400> 5  
ggggaaagtgc aggatggggg gacaggggacg ctccccgggg ggtggatgag ggaccatagc 60  
ggggctggcg gggcaggggc cggcgcacga ggctggagga ggggagcgcg cgcttctacc 120  
cgggctgggt cgccgagtc acagcctcga agccatgggt tctccccggc cctctgaagc 180  
cgccacacacct gtgccagccg gccgcgtcct cagaccttcc cccgcggagt cttcccagca 240  
cttggagacg cagcgcaggg cccggaggac ggcctggccc ggagaaaaaga taccgaagct 300  
ccaaaccttcc ccaaccccgc tcccttcctc cttccacccct ccctcccgcc ccccaaagct 360  
cgggggtcct atcccttcctc cggtccgcgg agtctcccga accctgcggg gaccgcgc 420  
tcggcggtgc ctcctgggg cgcacggggc tggggcggga gcgaggagac caggtgggg 480  
ggggacccca gatctcagac gcoaggggag acggcggttc ccgtgttca ttcagggtt 540  
tgccaaaagg agcctcacag atgcagtatt gggttggta gactcaaatc gtcttggttt 600  
aatgtaaatg aaagtaagtt taggataaat tccagtgcgg cggggcagg caaggctacc 660  
cacatTTTTT aaaaagaagc cagccccgtat ttttctccct ttccaaatcc tccgcgggg 720  
agtcccttcga cccaggcacg agcgccccatc gcggaggcca cgatgcccgt tttatccct 780  
ctccacggca aggaaaagca gcgaaatctg aggtcttcag aggttaaccc tatctaggag 840  
cagaatgtga cgcattgtaa acaaataaat attgaaaact cgatgttaaa a 891

<210> 6  
<211> 1253  
<212> DNA  
<213> Homo sapien

<400> 6  
gggaaagtgc aggatgggg gacagggcg ctcccgcccc ggtggatgag ggaccatagc 60  
ggggctggcg gggcaggggc cggcgcacga ggctggagga ggggagcgcg cgcttctacc 120  
cgggctgggt cgccgagtc acagcctcga agccatgggt tctcccccggc cctctgaagc 180  
cgccacacacct gtgccagccg gccgggttcct cagacccccc cccggggagt cttcccaagca 240  
cttggagacg cagcgcaggg cccggaggac ggcctggccc ggagaaaaaga taccgaagct 300  
ccaactttcc ccaacccccc tcccccttc cttccacacct cccttccccgc ccccaaagct 360  
cgggggtcct atcccttcctc cggccggcgg agtctccca accctgcggg gaccggcg 420  
tcggcggtgc ctcctgggg cgcacggggc tggggcgaaa gcgaggagac caggtgggaa 480  
ggggacccca gatctcagac gccaggggag acggcggttc ccgtgttca ttcatgggtt 540  
tgccaaaagg agcctcagat atgcagtatt gggtttgta gactcaaatac gtcttgggg 600  
aatgtaaaatg aaagtaagtt taggataaaat tccagtgcgg cggggcagg caaggctacc 660  
cacattttt aaaaagaagc cagccgtat tttctccct ttccaaatcc tccggcccccc 720  
agtccttcga cccaggcacg agcgccccatc gcggaggcca cgatgcccgt tttattccct 780  
ctccacggca aggaaaagca gcgaaatctg aggtcttcag aggttaaccc tatcttaggag 840  
cagaatgtga cgcattgtaa acaaataaaat attaaaaact cgatgttaaa cccttactt 900  
tttctgactc cgacttgctt gacccctgag cagacccccc tttcaacac agacgcccctt 960  
ccccatccctt ctattctctg tattccctgtt tcacccctcac agcagtctgc cagcactt 1020  
tagcactcag tttaaccaga gcacaagctc ctgaatagca aaaaccaggc cttttatac 1080  
gtggcacagt ggctgttaca aaatatgctt cttgggtgaa ttggtaaaaa atattgtatt 1140  
actttttatt tgtagcaaaa cctagaataa gaaaaagtac aagagattat tgtttgcctt 1200  
taaattgcattttaaaaga gcgtgcataat aatctctgag aaattaaatg tct 1253

<210> 7  
<211> 401  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (144)..(144)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (174)..(174)  
<223> n=a, c, g, or t

```
<220>
<221> misc_feature
<222> (304)..(304)
<223> n=a, c, g, or t

<220>
<221> misc_feature
<222> (383)..(384)
<223> n=a, c, g, or t

<400> 7
acgttcaaag caggcgaact tcatcatggt gtatggtata tgtctcatcc agagaggagc      60
aacccctat gtagaatgct tttagagcct tcttcctata tacatttctg ggagctgcat      120
ccactcaaag tgcttggcat aacnctggct ggcgttgca attacagaac cttnacgcag      180
cttccactag gcacgccagg agcaagtgtc acgcacaaga cattttcagc actggcagac      240
ggcatgccaa catatacgta catgctcgcg ccagagcata cagtattccc tcctaaagat      300
ccanacaaca caaggcaagg gcatgctgca attgcctgtt ggtgttaggt cttcacatt      360
cgacatgtga acagttctta gannacaaca acttaagctt g                                401

<210> 8
<211> 405
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (56)..(57)
<223> n=a, c, g, or t

<220>
<221> misc_feature
<222> (69)..(70)
<223> n=a, c, g, or t

<220>
<221> misc_feature
<222> (77)..(77)
<223> n=a, c, g, or t

<220>
<221> misc_feature
<222> (79)..(80)
<223> n=a, c, g, or t

<220>
<221> misc_feature
<222> (102)..(102)
```

<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (200)..(200)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (247)..(247)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (250)..(251)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (274)..(275)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (286)..(287)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (295)..(295)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (297)..(298)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (306)..(306)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (309)..(309)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (317)..(318)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (337)..(337)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (339)..(340)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (347)..(347)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (349)..(350)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (356)..(357)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (374)..(375)  
<223> n=a, c, g, or t

<400> 8  
actatTTaaa atgctcaatt tcagcaccga tggccatgt aataagatga tttaanntgt 60  
tgattttann atcctgnnnn atataaaata acaaagtac anatgagttt gggcatatTT 120  
aatgatgatt atggagcctt agaggtcttt aatcattggt tcggctgctt ttatgttagtt 180  
taggctggaa atggttcan ctgcgtcttt gacgtgtcac gcaagactga acgatagctt 240  
ttcctgngan ncagctagaa aacacaagaa tctnntgtag gtacannttg caccnntnat 300  
ctcagncgnc ataggtnngc agtcttcgct tctacantnn gatgctnann aaggcnntgc 360  
gaactgcgga ctcnntgat gcgacactaa ggactccaaat gtcga 405

<210> 9  
<211> 305  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature

<222> (1)..(19)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (286)..(305)  
<223> n=a, c, g, or t

<400> 9  
nnnnnnnnnn nnnnnnnnnnt aaaaagaaaa aaggaaactg gttacacatc tgtccacaaa 60  
ggcaaatgca ggggggctgg tgactcctgg gtataaaggc tcacatctgt ttatgttaat 120  
taagagagca gtatgttaacc agtatcattc cacttcagtt ttcttttagg atctaacata 180  
gtgctatcca agagatatat aatataatgc cacatgttat atttcctgat agcctcattt 240  
tataaaagtag tccaatgctt cactcagcca ttttacctca cccccnnnnn nnnnnnnnnn 300  
nnnnn 305

<210> 10  
<211> 299  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (280)..(299)  
<223> n=a, c, g, or t

<400> 10  
ggagtgtgct tgtggccct cagaaagata gtctgctggc tcctaggggt tggggtgtggg 60  
gacacacacctt tttctcagga agaggtgatg gcaatgtaaa acatctaagc aaagttttaa 120  
atgaaaaaaaaa ggaaacacat ttaaacatcc tgataatgga gggaaaggggg gcacatttac 180  
acatagccca gaactttag aattctgcat agtgaatgta tattgaatta gtctcctgcc 240  
ttatacattc aggaggaata aattccata atgtaaaggcn nnnnnnnnnn nnnnnnnnn 299

<210> 11  
<211> 1249  
<212> DNA  
<213> Homo sapien

<400> 11  
tagctccttc caactcctca gaatctccac totatggatc tggacctctg gattcggtt 60  
tctccctggg cactgccttc aggaagacgt tgagaattga ctttacacaa tcccagcgcc 120  
ctcctcacag gagccttca ctttacagtg gcaaggggcc tggttctgga gaactggctg 180  
atgctctgaa tttcttcata tacccacat ttgactttgg cttacactgt acaattggag 240

10

atgttgctac	aggtccctga	gatgcaatca	gattaagcgt	agcaaggcatt	gccaatggga	300
aagtcaaaaat	aatttatttt	tttcccttt	ccccctaccc	catccccagc	caagaatttc	360
tttcaagat	atcgtcatca	ttcttaaaca	acattctaa	cccccagctg	gggtccccat	420
tttaatagat	gtcattgctt	caagtctaac	ggcgccggga	ggcctgtttg	agggaaaaca	480
ttagttgaa	aaatccccgt	tcccttcate	cactgcctt	gttctccacg	tgggagtg	540
cttgtggccc	ctcagaaaga	tagtctgctg	gctcctaggg	gttgggggtgg	gggacacacc	600
tttttctcag	gaagagggtga	tggcaatgta	aaacatctaa	gcaaagttt	aaatgaaaaaa	660
aaggaaacac	attnaaacat	cctgataatg	gagggaaggg	gggcacattt	acacatagcc	720
cagaacttgt	agaattctgc	atagtgaatg	tatattgaat	tagtctcctg	ccttatacat	780
tcaggaggaa	taaatttcca	taatgttaagg	caaatgcatt	gggttctgag	gttcactttg	840
caagtgcctt	tgctgcctt	cctctgtgtc	tattatggct	ctttaagttg	acggttcctg	900
gagcagctt	tattnagttt	cgttggcag	tctggccctg	ttgactttga	tttgcagacc	960
aattctccct	tgacctgact	cacagccgccc	tgctcttacc	cccctcctca	ggaagtcttc	1020
ctcattaaag	gatgtgatga	cggagctcag	ggatgagaat	gcacatgtga	gactgtgtga	1080
caccaaggag	ggttgtgcga	actggtgaca	acatggcagc	accatggcct	gtgggggttg	1140
tgtgactagt	gtgactgtgc	tggcgaccat	atggacctgt	tttgcagtc	ggtgtctaag	1200
caggagatgg	cacactcaaa	ctggaaagtg	ttttaaacat	aggctattc		1249

<210> 12  
<211> 236  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (217)..(236)  
<223> n=a, c, g, or t

<400> 12	tggccagaat	cccccagaga	atcagggacc	agctttactg	gagttggggg	cggttgtct	60
	tcgctggctc	ctaccccatc	tccaagataa	gcctgagcct	tagtcccag	ctagggggcg	120
	ttattnatgg	accacttta	tttattgtca	gacacttatt	tattggatg	tgagccccag	180
	ggggggctcc	tcctaggata	ataaaacaatt	ttgcggnnnn	nnnnnnnnnn	nnnnnn	236

<210> 13  
<211> 3218  
<212> DNA  
<213> Homo sapien

<400> 13  
cccgggcaaa agcgagcgc gcccctgcct ctccgctgct ggctggaaacg ctgatctatc 60  
tagttgctgg ggagacgccc ccagatgccc gggccccact cggaacttcag cacacatccc 120  
gaaggatggg gaaaagaaaaga ggcccccaacg agcgggactc gcagtggcca aggaggggtg 180  
agaggcggac agggatcagc tggcccctgc ggcctggtg cacctgcattg gtgacttagct 240  
gccgggctgc gccccggggc gcggcgagga ggccccgtct ggcagtgcgt tgggtggggg 300  
aggagcttct gggtgatgta aggccggaa tgggagtggg cctctcctcg actcgctgct 360  
aggaaggggg cgggactctc ggtgaccaga cgccggggag ggggcaggcg ttcattgata 420  
aaacgctggg ctccccctggg cgccagcgca gcgttagcaaa tccagggcagc gccacgcgcg 480  
gccggggccg ggccgaaccg agaagccggg accgcgtgc gacgcgcggc ccgcattggag 540  
cctgcgcgcg gtttccctgtc tccgcgcggc ttccagcgtg cggccgcgcg gcccgtccc 600  
ccggccgggc ccggccggcc tccgagtgcc ttgcgcggac ctgagctgga gatgctggcc 660  
gggctaccga cgtcagaccc cgggcgcctc atcacggacc cgccgcggcc ccgcacctac 720  
ctcaaaggcc gcttggggg caaggggggc ttgcggccgt gctacgaggc cactgacaca 780  
gagactggca gcgcctacgc tgtcaaagtc atcccgaga gccgcgtgc caagccgcat 840  
cagcgcgaga agatcctaaa tgagattgag ctgcaccgag acctgcagca ccgcacatc 900  
gtgcgtttt cgcaccactt tgaggacgct gacaacatct acatttctt ggagctctgc 960  
agccgaaagt ccctggccca catctggaaag gcccggcaca ccctgttggg gccagaagtg 1020  
cgctactacc tgcggcagat ccttctggc ctcaagtact tgcaccagcg cggcatcttgc 1080  
caccgggacc tcaagttggg aaatttttc atcaactgaga acatggaaact gaaggtgggg 1140  
gattttgggc tggcagcccg gttggagcct ccggagcaga ggaagaagac catctgtggc 1200  
accccaact atgtggctcc agaagtgcgt ctgagacagg gccacggccc tgaggcggat 1260  
gtatggtcac tggctgtgt catgtacacg ctgctctgcg ggagccctcc ctggagacgc 1320  
gctgacactga aggagacgta ccgctgcatac aagcagggtc actacacgct gcctgcgc 1380  
ctctcactgc ctgcccggca gtcctggcc gccatccttc gggcctcacc ccgagaccgc 1440  
ccctctattg accagatctt ggcgcatttgc ttctttacca agggctacac ccccgatcga 1500  
ctccctatca gcagctgcgt gacagtccca gacctgacac cccccaaccc agctaggagt 1560  
ctgtttggca aagttaccaa gagcctttt ggcagaaaga agaagagtaa gaatcatgcc 1620  
caggagaggg atgaggtctc cggtttggtg agcggcctca tgcgcacatc cggtggccat 1680  
caggatgccca ggccagagggc tccagcagct tctggcccaag cccctgtcag cctggtagag 1740  
acagcacctg aagacagctc accccgtggg acactggcaa gcagtggaga tggatttgaa 1800

12

gaaggctctga	ctgtggccac	agtagtgag	tcagccctt	gtgctctgag	aaattgtata	1860
gccttcatgc	ccccagcgg	acagaacccg	gcccccctgg	cccagccaga	gcctctgg	1920
tgggtcagca	agtgggtga	ctactccaat	aagttcggt	ttgggtatca	actgtccagc	1980
cggcgtgtgg	ctgtgcttt	caacgatggc	acacatatgg	ccctgtcggc	caacagaaaag	2040
actgtgcact	acaatcccac	cagcacaaaag	cacttctcct	tctccgtggg	tgctgtgccc	2100
cgggcccctgc	agcctcagct	gggtatcctg	cggtaacttcg	cctcctacat	ggagcagcac	2160
ctcatgaagg	gtggagatct	gcccagtg	gaagaggtag	aggtacctgc	tccggcccttg	2220
ctgctgcagt	gggtcaagac	ggatcaggct	ctcctcatgc	tgtttagtga	tggcaactgtc	2280
caggtgaact	tctacgggga	ccacaccaag	ctgattctca	gtggctggga	gccccctcctt	2340
gtgacttttg	tggcccgaaa	tcgttagtgct	tgtacttacc	tcgcttccca	cttcggcag	2400
ctgggctgct	ctccagacacct	gcggcagcga	ctccgctatg	ctctgegect	gctccgggac	2460
cgcagccca	cctaggacccc	aagccctgag	gcctgaggcc	tgtgcctgtc	aggctctggc	2520
ccttgcctt	gtggccttcc	ccttccctt	ggtgccctcac	tggggcttt	ggccgaatc	2580
ccccagggaa	tcagggacca	gctttactgg	agttggggc	ggcttgtctt	cgctggctcc	2640
taccccatct	ccaagataag	cctgagcctt	agctcccagc	tagggggcgt	tatttatgga	2700
ccacttttat	ttattgtcag	acacttattt	attggatgt	gagccccagg	ggggcctcct	2760
cctaggataa	taaacaattt	tgcagaaaaaa	aaaaacaaca	aaacaaaaaa	acaaaacaga	2820
agcacacaac	caccacacaa	cacgaggggc	cccaaccaag	agaccaaccc	acaaccgagc	2880
ccacaaacag	agggacgcga	cacaccgcac	acgacacagg	caagagcggg	cgcacccaca	2940
acggaccgccc	cgcacacgggc	agaggcagcg	agggacgcac	agatacacag	aggaggaggc	3000
gagagaaaaag	ggaggagagg	agagaacaac	agaggagggc	gaacacgacg	cccgccggaga	3060
caagcggaggg	cggccacacc	caccaagagg	agaccggaca	accgggaga	aaacaaccgc	3120
gacagcgcaca	ggagggcgcc	agagaggcag	acacagagcg	cagcgcggca	cagagcgcgg	3180
cgggagccgc	cgagcgcacca	gtacaacagg	aacagcaa			3218

<210> 14  
<211> 501  
<212> DNA  
<213> Homo sapien

```
<220>
<221> misc_feature
<222> (84)..(84)
<223> n=a, c, g, or t
```

<220>

<221> misc\_feature  
<222> (137)..(137)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (146)..(147)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (160)..(161)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (169)..(170)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (181)..(181)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (183)..(184)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (195)..(196)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (205)..(206)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (211)..(212)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (219)..(221)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature

<222> (227)..(228)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (234)..(234)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (236)..(236)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (238)..(238)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (241)..(243)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (249)..(249)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (252)..(253)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (256)..(256)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (259)..(259)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (261)..(262)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (267)..(267)

<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (271)..(271)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (273)..(273)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (275)..(275)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (278)..(278)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (280)..(281)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (284)..(284)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (287)..(287)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (289)..(289)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (291)..(292)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (296)..(297)  
<223> n=a, c, g, or t

```
<220>
<221> misc_feature
<222> (303)..(303)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (305)..(305)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (308)..(308)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (310)..(310)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (312)..(312)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (315)..(315)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (317)..(318)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (322)..(322)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (324)..(324)
<223> n=a, c, g, or t
```

```
<220>
<221> misc_feature
<222> (327)..(329)
<223> n=a, c, g, or t
```

<220>  
<221> misc\_feature  
<222> (336)..(336)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (338)..(339)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (344)..(345)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (349)..(349)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (351)..(351)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (353)..(353)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (356)..(356)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (358)..(358)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (360)..(360)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (362)..(362)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (367)..(367)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (369)..(369)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (371)..(371)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (373)..(373)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (375)..(375)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (377)..(377)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (380)..(380)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (382)..(383)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (389)..(389)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (391)..(391)  
<223> n=a, c, g, or t

<220>

<221> misc\_feature  
<222> (393)..(393)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (396)..(396)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (398)..(398)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (402)..(402)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (404)..(404)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (406)..(406)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (408)..(408)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (410)..(410)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (412)..(412)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (414)..(414)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature

<222> (416)..(416)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (421)..(421)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (437)..(437)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (447)..(447)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (453)..(453)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (455)..(455)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (459)..(459)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (461)..(461)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (463)..(463)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (467)..(468)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (471)..(471)

<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (473)..(473)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (475)..(475)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (477)..(477)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (479)..(479)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (481)..(481)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (483)..(483)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (485)..(485)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (487)..(487)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (489)..(489)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (491)..(491)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (493)..(493)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (497)..(497)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (499)..(499)  
<223> n=a, c, g, or t

<400> 14  
acaggccgac agagaagatt cccgagagta aatcatcttt ccaatccaga ggaacaagca 60  
tgtctctctg cgcaagatcc atcntaaact ggagttagtg ttagcagaac ccgagcttag 120  
aagttctcta ctttcgnntt cttaanngcc ctttgcctgn ntggaggann agttctccag 180  
ncnnttcacg ctcannactc acagnncttc nntccaagnn ncatcanncc ctgngngnag 240  
nnntttccnt gnnagnggnt nnnttcntac nanthaanan ntgnagngng nnctgnncac 300  
tantntgnncn cntgntnnnc tngnctnnnt cgcaangnnt attnncaant nanccngncn 360  
tncacgnntna ntntntntan annactagna nangcntngc antntncntn anangncact 420  
nttcggcgct ctctcgngcg cactacnaca ctnangagna nanacgnnca ntnantngnc 480  
nangncncna nancacnana g 501

<210> 15  
<211> 569  
<212> DNA  
<213> Homo sapien

<400> 15  
acagaacatg atcaagggtg ttacactggg cttccgttac aagatgaggt ctgtgtatgc 60  
tcacttcccc atcaacgtat gttatccagg agaatgggtc tctttagaa atccgaaata 120  
tcttgggtga aaaatatatac cgccagggttc ggatgagacc aggtgttgct tggtcagttat 180  
ctcaagccca gaaagatgaa ttaatccttg aaggaaatga cattgagcta gtttcaaatt 240  
cagcgtgctt tggatgtcag cagatgccac aatcagttaa gaacaaggat atcaggaaat 300  
ttttggatgg tatctatgtc tctgaaaaag gaactgttca gcaggctgat gaataagatc 360  
taagagttac ctggctacag aaagaagatg ccagatgaca cttaagacct acttgtgata 420  
tttaaatgat gcaataaaag acccattgat ttggaccttc ttcttaaaaa aaaaaaaaaaca 480

aaaaaaaaaaa aagccggggg aaaacagggg ccaaggggtt cccgggtgga cattgtttcc 540  
 ggcccaattt cccacattt ggacaaaat 569

<210> 16  
 <211> 971  
 <212> DNA  
 <213> Homo sapien

<400> 16  
 atgaagacta ttctcagcaa tcagactgtc gacattccag aaaatggtat gagacttgat 60  
 gtctttact tacatctta ctgcacgttc caagcggtgt gtggcctgac gagtggtgtc 120  
 tctttcttag tcgacattac tctgaaggaa cgcacagta tcgtgaaggg ccccagagga 180  
 accctgcgga gggacttcaa tcacatcaat gtagaactca gccttcttgg aaagaaaaaa 240  
 aagaggctcc gggttgacaa atgggtgggt aacagaaaagg aactggctac cgttcggact 300  
 attttagtc atgtacagaa catgtcaag ggtgttacac tgggcttccg ttacaagatg 360  
 aggtctgtgt atgctcaett ccccatcaac gttgttatcc aggagaatgg gtctttgtt 420  
 gaaatccgaa atttcttggg tgaaaaatat atccgcaggg ttcggatgag accaggtgtt 480  
 gcttgcag tatctcaagc ccagaaaagat gaattaatcc ttgaaggaaa tgacattgag 540  
 cttgttcaa attcagcggc tttgattcag caagccacaa cagtaaaaaa caaggatatc 600  
 agggaaatttt tggatggtat ctatgtctct gaaaaaggaa ctgttcagca ggctgatgaa 660  
 taagatctaa gagttacctg gctacagaaa gaagatgcc aatgacactt aagacactt 720  
 tgtgatattt aaatgtatgca ataaaagacc tattgattt gaccccttcc ttaaaaaaaaag 780  
 aaaaaaaaaaaaaga caaagaacaa catagagcaa aaacgagcaa gcaaaaaaca gaagaacaca 840  
 gccccggcg attttattgt tggcgcccg gcgcaaaacc agggcctcag tcaacggcca 900  
 ggttgccata ggggtgtccc gccccctttt ttttccccga gtgcgaacac ccggcgcccc 960  
 aatgagggac a 971

<210> 17  
 <211> 422  
 <212> DNA  
 <213> Homo sapien

<400> 17  
 acaactccaa aaggagacat tggagaagaa ccaagctggg tctataagga attgcacatg 60  
 agatggcaca catatttatg ctgtctgaag gtcacgatca ttttaccata tcaagctgaa 120  
 aatgtcacca ctatctggag atttcgacgt gtttcctct ctgaatctgt tatgaacacg 180  
 ttggttggct ggattcagta ataaatatgt aaggccttcc ttttaaaaaa aaaacaacaa 240

24

aaaaaaaaaaa	aaaaaaaccc	ctggggcgta	ccccggggca	aaagggtggt	ccacggggtg	300
agacttggtt	ccccggcgca	aaatcccccc	acactactaa	gaacaagagg	gccacggagg	360
agcagcacgc	acagatcaca	gcagaccgac	acagatagca	acacagagac	acacacgcac	420
ag						422

<210> 18  
<211> 584  
<212> DNA  
<213> Homo sapien

<400> 18	aagaattcac	tagtaatcgc	catcgtggtg	tgttcttgac	tccgctgctc	gccatgtctt	60
	ctcacaagac	tttcaggatt	aagcgattcc	tggccaagaa	acaaaagcaa	aatcgtccca	120
	ttccccagtg	gattcggatg	aaaactggaa	ataaaatcg	gtacaactcc	aaaaggagac	180
	attggagaag	aaccaagctg	ggtctataag	gaattgcaca	tgagatggca	cacatattta	240
	tgctgtctga	aggtcacgat	catgttacca	tatcaagctg	aaaatgtcac	cactatctgg	300
	agatttcgac	gtgttttct	ctctgaatct	gttatgaaca	cgttggttgg	ctggattcag	360
	taataaaatat	gtaaggcctt	tctttttaaa	aaaaaaaaaaa	aaaaaaaaaaa	aaaaaaaaaac	420
	ccctggggcg	taccccgggg	caaaagggtg	gtccacgggg	tgagacttgg	ttccccggcg	480
	caaaatcccc	ccacactact	aagaacaaga	ggccacgga	ggagcagcac	gcacagatca	540
	cagcagaccc	acacagatag	caacacagag	acacacacgc	atag		584

<210> 19  
<211> 747  
<212> DNA  
<213> Homo sapien

<400> 19	acaatattga	acattttct	atatccttg	atatctgcaa	gcctgatttt	cagtagctgg	60
	aaatggaaag	gccaaattta	ttatctaatt	ttatacatta	ggacatgtgt	ataatgtcca	120
	atttataact	gttataagtc	acactatgat	gaacatttt	gtacataact	aaccatattt	180
	cagttcattt	ctttaggtta	ttatatatcc	acagatatga	cattcaattc	tataaaaatt	240
	atgtacattt	taatttattt	tattttgta	catggaaagc	tcctatctta	actcattaaa	300
	ttcaataaaat	tttgttatttc	tacaacagaa	agccaacaaa	gggagttgtt	agtacatatt	360
	tccaggaatg	aagttgtctg	gatgcagcta	atgcctccat	agaactgaca	gtgctgaatt	420
	tacgaaatgg	aaagagttct	ggaaaagcaa	gaaaaaaaaagt	cttggggaa	accccacgac	480
	tactgttaggc	acagaaggga	atggaggcat	ctgagcattt	tatttccat	ctctacagca	540
	cctcagaaca	cctacatttt	atttttttc	ttctcagaaa	tgtcttaata	agaggactgc	600

agtgtactca agtttcccaa tgacaggta gggatgccaa cttctcttt cattggcagc 660  
tcatagtatac caagttctc aaaaccctaa gccatcttat ttgttcttg gaacttttg 720  
gcctaccaca gtgcaatctc atcggtg 747

<210> 20  
<211> 766  
<212> DNA  
<213> Homo sapien

<400> 20  
acaatattga acattttct atatccttg atatctgcaa gcctgattt cagtagctgg 60  
aaatggaaag gccaaattta ttatctaatt ttatacatta ggacatgtgt ataatgtcca 120  
atttatact gttataagtc acactatgat gaacatttt gtacataact aaccatattt 180  
cagtcattt cttaggta ttatatatcc acagatatga cattcaattc tataaaaatt 240  
atgtacattt taatttat tattttgtt catgggaagc tcctatctt actcattaaa 300  
ttcaataaat tttgtatssc tacaacagaa agccaacaaa gggagttgtt agtacatattt 360  
tccaggaatg aagttgtctg gatgcagcta atgcctccat agaactgaca gtgctgaatt 420  
tacgaaatgg aaagagtct ggaaaagcaa gaaaaaaagt cttgtttgaa accccacgtc 480  
tactgttaggc acagaaggaa atggaggcat ctgagcattt tattttccat ctctacagca 540  
cctcagaaca cctacatttt attttttcc ttctcagaaa tgtcttaata agaggactgc 600  
agtgtactca agtttcccaa tgacaggta gggatgccaa cttctcttt cattggcagc 660  
tcatagtatac caagttctc aaaaccctaa gccatcttat ttgttcttg gaacttttg 720  
gcctaccaca gtgcaattct cattcggtgt ttaataactc gagccg 766

<210> 21  
<211> 647  
<212> DNA  
<213> Homo sapien

<400> 21  
tgaacatcat catgaataaca tgaatcggt gtgatgtgt aactgctaag ggccaaatga 60  
acgtttgcag agcagtgggc acaatgttta caatgtatgt gtatgtcact ttcggcacct 120  
gtgaatgcat ggggacgtgc tgaacccgaa aaaaagtgcc tttccataag gactgcaata 180  
gagagggcaa tttaccctgg tggtacacgg aacctagatt cactcctgcc atgccttgcc 240  
aatagtaagc tgcaggggtgg aacaagaaaat cacttgctct ggggggaagg gaggggggaa 300  
tgggtgtgtc agctgggttag atacaaaccc tggaaaagaga atccatgtgc tgctggcagg 360  
caacatttt taaagctctt tcagaaaccc tcataattgg ggtttcttt cagggaaacat 420

26

tcctgtggag ggaaaacgaa tatgaagata atttcagct aattatctgg gtgaccaga 480  
atcggtata tggctatagg atagacttct taataatggc aagtgaegtg gccctggga 540  
aagggtctt atgtaccgtg tgtgcgtgta tgtgtgtgta tctataacaag tttgtcagct 600  
ttggcatgac tgtttgttg tctcgaaaac caataaactc aaagttt 647

<210> 22  
<211> 698  
<212> DNA  
<213> Homo sapien

<400> 22  
actagcacccg ggcaagcaga caacataatt tattccaga aaacaacaga atgaacatca 60  
tcatgaatac atgaatccgc tgtgatgtgt gaactgatcaa gggccaaatg aacgtttgc 120  
gagcagtggg cacaatgttt acaatgtatg tgtatgtcac ttccgttacc tgtgaatgca 180  
tggggacgtg ctgaacccga aaaaaagtgc cttccataa ggactgcaat agagaggc 240  
atttaccctg gtggtacacg gaaccttagat tcactcctgc catgccttgc caatagtaag 300  
ctgcagggtg gaacaagaaa tcacttgctc tggggggaaag ggagggggga atgggtgtgt 360  
cagctggta gatacaaacc ctgaaaagag aatccatgtg ctgctggcag gcaacattt 420  
ttaaagctct ttcagaaacc ctcataattt gggtttcttt tcaggaaaca ttctgtgga 480  
gggaaaacga atatgaagat aatttcagc taattatctg ggtgaccagg aatcggtat 540  
atggctatag gatagacttc ttaataatgg caagtgaegtg gccctgggg aaaggtgctt 600  
tatgtaccgt gtgtgcgtgt atgtgtgtgt atctatacaa gtttgcgtc tttggcatga 660  
ctgtttgttt gtctcgaaaa ccaataaact caaagttt 698

<210> 23  
<211> 739  
<212> DNA  
<213> Homo sapien

<400> 23  
taaacttaag gctaattttt agaagctttt gctaattgaga ggaccatttg ctaaatcggt 60  
ataagtgcata cacatttggg tatctccatc ccaacatacc tcttattgcc attccccaaa 120  
gcagacaccg tctcccccct ccctcaagga cctctgagct tgcaactccaa ttccctctccc 180  
acactcacct ttctcccttc tgttccctttt gggatccagg tttatttgag gagataggaa 240  
aagctccctga tccagcaggt tttattctta aatttgtaac aaagtaaatc acagaacctc 300  
caccctgcac cacatagacc ctgggcctga attgtgtga gtaataatga ctctgtcg 360  
aatttggtc cttctgttg gaactgtttc cttttagttt tggtcaccct cccagagctg 420  
480

gtttcaatgg gggcatacc accattatggat gcagggcatc ctgcacatcctg aggaattttt 540  
tttcctccaa aaatgaaacc ttgaaatgag gacattgtcc tgtccacgga ctgcacaaca 600  
acactgagcc tcaaggactc atactggcat ttttcttctt ttgcagagtg tgggcacccct 660  
ggcttcaagc tcacgagaaa ccaggtcgaaa atttaaacaa tgttgggtt aagcaaagtt 720  
tcataaagac agaatcaag 739

<210> 24  
<211> 900  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (75)..(75)  
<223> n=a, c, g, or t

<400> 24  
agcacatcc ggcacgagta cgtaatatac tccagtttgc aaatgaagga atcttcctgc 60  
ggaacgtatg tgaangcata ttggtgctct gggcttttgc ataatttcaa atgtcctttt 120  
tttttaaact taaggcta at gtgtagaagc ttttgcta at gagaggacca tttgctaaat 180  
cggtataagt gctacacatt tggtatctc catcccaaca tacctctt at tgccattccc 240  
caaaggcagac accttctcctt ccctccctca aggacctctg agcttgcact ccaattcctc 300  
tccccacactc acctttctcc tttctgttcc tcttggatc caggttatt tgaggagata 360  
ggaaaaagctc ctgatccagc aggtttattt cttaaatttgc taacaaagta aatcacagaa 420  
cctccaccca gcatccagggc ctctggttctt ctccctcctt cccaggtata ggccggcttt 480  
cagaaaacctt gcaccacata gaccctgggc ctgaatttgc gtgagtaata atgactctgc 540  
tcgtaatttgc tgccttctg cttggaaactg tttcctttt agttggatc ccctccca 600  
gctggttca atggggcat acccattatg ggtgcaggg catcctgc at cctgaggaat 660  
ttttttctt ccaaaaatga aaccttggaa tgaggacatt gtcctgtcca cggactgcac 720  
aacaacactg agcctcaagg actcataactg gcattttctt tctttgcag agtgtggca 780  
ccctggcttc aagctcacga gaaaccaggt cgggatttac acaatgttgg gttaaagcaa 840  
agtttcataa agacagaatc aagaaaaaaaaaaaaaaa atatactggc cgcaaggaat 900

<210> 25  
<211> 299  
<212> DNA  
<213> Homo sapien  
  
<400> 25

ggcagcgccgg aggccgcacg atgcctggag ttactgtaaa agacgtgaac cagcaggagt 60  
tcgtcagagc tctggcagcc ttccctaaaaa agtccggggaa agctgaaagt ccccgaatgg 120  
gtggataacc gttcaagctg gccaaagcac aaaggagctt gctccctacg atgagaactg 180  
gttctacacg cggagctgct ttccaacagc ggcgggcccc ac ctgttacctt ccgggggtgg 240  
gcgctgggggg ttgggcttcc attgaaccca aggattctat tgggggggaa cgttcagaa 299

<210> 26  
<211> 1346  
<212> DNA  
<213> Homo sapien

<400> 26  
ttttttttt ttgtgagcca gtggggaaaac caaggaggct aaaccataga gcctggagat 60  
gtgaaggaag tacaggtggg taagaaaggg agagccagat cacaagcacc ttgaaaccag 120  
acactggttt ggggtcttca gcagtcctct gtcgaaatac atatattcag gggctgggtg 180  
tggtggtca cacctgtaat cccagccctt tgggaggcag aggcaggcag attactttag 240  
gtcaagagtt caagacaagc ctggccaaca tggtaaaacc ccgtctctac caaaaatata 300  
aaaaactagc cgggcgtgggt ggcaggcacc tgattgtaat cccagctact cgggaggctg 360  
aggcaggaga atcatttcaa cccagaaggc ggagattgca gtgagctgag atggcgccac 420  
tgccactccc agcctggcgc acagagcaag agactcaaaa aagagaccca gaccaggatt 480  
acgaatgagg caatttatta acccagcatg gtttgttcta atgcttcttgc ttggcagctg 540  
ccacctgtcc ggcgattctg tccagatctc tttgtccctg aggtgtcagt ttgcggccgc 600  
catcttggtc cttttccacc atttcagcc cctccaggggc ttggaggacc cggcgggcca 660  
caacttttggaa gcctcggctg aagtggctgg gcatgacgcc gtttctctga cgtccccat 720  
agatcttgggt catggagcca accccagcgc caccggag gtacaggtgc cgcgcgtgtgg 780  
aagcagctcg cgtgtagaac cagttctcat cgtagggagc aagcttttg tgcttggcca 840  
gcttgacggt atccacccat tcggggactt tcagcttccc ggacttttg aggaaggctg 900  
ccagagctct gacgaactcc tgctggttca cgtctttac agtaactcca ggcacatcg 960  
ggcctccgcg ctgccagcca ggggaaaggg aacgacgggg tttccgggc gcacaagtcg 1020  
ggcgttagggt ctcgcgagag ttccgaaagc tcgcgagagc gagggtagac gctgaggctc 1080  
cgcctctctc agggcgaaag ttctgtccccg cctagagggg agggtgtcta gtgaggggtg 1140  
gagaggtaaa ggggaggggcc aaggggtcgc gcgtggaggg ctgggtttcc tcccgcttt 1200  
ccttctcccg gagtgtataa gagagaggat agagagctcc tgctcggagc tgggggaact 1260  
tggcttcgtt tgctcggttc gtggctggaa ggaacagtgg tggagaatac tatgtatggcg 1320

aaagtacggg gcaggatggg tgggcc

1346

<210> 27  
<211> 136  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (75)..(75)  
<223> n=a, c, g, or t

<400> 27  
gtcgccgctg cgaagggagc cgccgcattg tctgcgcattc tgcaatggat ggtcgtgcgg 60  
aactgctcca gtttntgtat caagaggaat agccccctgc ccccagagca ataaaagtcag 120  
ctggctttct cacctg 136

<210> 28  
<211> 426  
<212> DNA  
<213> Homo sapien

<400> 28  
gctcgaggcc atttcctctc tccagaggac ctccctgcc taggactcat cattgtcccc 60  
tccctggcat tttttacacc tggagcagcc agaggacgca tgcatggctc ttggaaagcc 120  
ttccctgcc acggcatgca cccacacatg cgagcctccc gggtaactgtc atcctgaatt 180  
ctgagaccat ccagcacttc cttagttt gccctggtgc ttttgacttt ttgttactga 240  
agagtgtgct ggaggcagga caagggacat ggaaggctgc aatttaagag tctaaaaggt 300  
tttagaatcc tgaaggaggt ttaacaagct gaattgaaga ataatacctt tctcaactgg 360  
agagaattta catgattgca ttattgttaa aattaacatc tcatttattt aaagcatttg 420  
tagatt 426

<210> 29  
<211> 364  
<212> DNA  
<213> Homo sapien

<400> 29  
cgggAACCT gagacctctc cagcgaagct gaagtgcgtgt gttacgggag agagtgactg 60  
gaaagtaaca aagctgaatc ttccctctg gagtaaggcc gaagactggta ttactacacg 120  
ccttagacgtg acactacacc catagatctc atgcatttattt aatgccatat gacattgcc 180  
ttttctttct cagttcacgg acaaaagtgg tgggtttca ttgcttcaact gattgtcaat 240  
gcatttaataa agaagatgtg tggt 264

<210> 30  
<211> 265  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (164)..(164)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (168)..(168)  
<223> n=a, c, g, or t

<400> 30  
cgcccttctt gtaagaaaga tccacggccg ggcccgccg gccccgttc ccagagactc 60  
atccagccgg aggagatgtg gctctaccgg aaccctacg tggaggcgga gtatccccc  
accaagccga tgtttgtcg tggagaaaga tcgtcttcc tcncntcnca tgaccggct 120  
tcccgccggc acctgtgcgt ttccacccc gagacggcct ttgttattgc atttctctct 180  
ccactgtctc tgatcttctt ggcca 240  
265

<210> 31  
<211> 741  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (718)..(718)  
<223> n=a, c, g, or t

<400> 31  
ggcaaccaca ggttccaaga tggtttgcgg gggcttcgcg tgttccagtc tccgagtgg 60  
cggcgtggc attgcagtgg gcatcttctt gttcctgatt gcttagtgg gtctgattgg  
agctgtaaaa catcatcagg tggtgttatt cttttatatg attattctgt tacttgatt 120  
tattgttcag ttttctgtat cttgcgcctg tttagccctg aaccaggagc aacagggtca 180  
gcttctggag gttgggttgg acaatacggc aagtgcgtcg aatgacatcc agagaaatct 240  
aaactgctgt gggttccgca gtgttaaccc aaatgacacc tgtctggcta gctgtgtt 300  
aaatgtgtt ggtggcattg gcctgttctt cagtttaca gagatcctgg gtgtttggct 360  
aagtgaccac tcgtgctcgc catgtgctcc aatcatagga gaatatgctg gagaggttt 420  
gagatttgg tggcattg gcctgttctt cagtttaca gagatcctgg gtgtttggct 480  
gacctacaga tacaggaacc agaaaagaccc ccgcgcgaat cctagtgcatt tcctttgatg  
agaaaaacaag gaagatttcc ttctgttatta tgatcttggt cactttctgt aattttctgt 540  
600

taagctccat ttgccagttt aaggaaggaa acactatctg gaaaagtacc ttattgata 660  
tggaattata tatcaccta gtttctctac agttttcttc cgtgcgaaaa atattganac 720  
tgggcctgaa ccggggcacg g 741

<210> 32  
<211> 1844  
<212> DNA  
<213> Homo sapien

<400> 32  
aaggatcctt aattaaatta atccccccc cccgctcctt gccagcgtgg atctcctccg 60  
agccccggcc tccctcctca cctgctcctg gggaaactac accaaggccg cgcctctggc 120  
ctggggctcc ctccccacacg gccttggccc tctccccctc gccccgggac cgctccgccc 180  
ctcccgatc cgggtcggcg gagcgcattt atttgcatat ttctaccttt gttccccgcc 240  
tggccaggc cccaaaggca aggacaaagc agctgtcagg gaacctccgc cggagtcgaa 300  
tttaegtgc agtgcggca accacaggtt ccaagatggt ttgcggggc ttcgcgtgtt 360  
ccaagaactg cctgtgcgc ctcaacctgc tttacacctt ggtagtctg ctgctaattg 420  
gaattgctgc gtggggcatt ggcttcggc tgatttccag tctccagtg gtcggcgtgg 480  
tcattgcagt gggcatcttc ttgttcctga ttgcttttgtt gggtctgatt ggagctgtaa 540  
aacatcatca ggtgttgcta ttctttata tgattattct gttacttgta tttattgttc 600  
agtttctgt atcttgcgt ttttagcccc tgaaccagga gcaacagggt cagttctgg 660  
aggttgggtt gacaataac gcaagtgc gaaatgacat ccagagaaat ctaaactgct 720  
gtgggtccg aagtgttaac ccaaatacaca cctgtctggc tagctgtttt aaaaagtgacc 780  
actcgtgc cccatgtgct ccaatcatag gagaatatgc tggagagggtt ttgagatttg 840  
ttgggtggcat tggcctgttc ttcaatggc cagagatctt gggtgtttgg ctgacctaca 900  
gatacaggaa ccagaaagac ccccgccaa atcctagtgc attccttgc tgagaaaaca 960  
aggaagattt ccttcgtat tatgatcttgc ttcaatggc gtaatggc tttaagctcc 1020  
atggccagt ttaaggaagg aaacactatc tggaaaagta ctttattgtt agtggaaatta 1080  
tatatggat cttatgttt ctctacatgt tttttctt ccgttgctga aaaatatttgc 1140  
aaacttgcgtt tctctgaaac tcgggtggcac ctggaaattt ctgtattcat tgcgggac 1200  
tgtccactgt ggcctttttt agcatttttgc cctgcagaaaa aactttgtt ggtaccactg 1260  
tgttggttt atgggtgaatc tgaacgtaca tctcaactggt ataattatat gtagcactgt 1320  
gctgtgtaga tagttccat tggaaaaaga gtggaaattt attaaaatca gaaagtatga 1380  
gatcctgtta tgttaaggaa aatccaaatt cccaaattttt tttggcttt ttaggaaaga 1440

tgtgttgtgg	taaaaagtgt	tagtataaaa	atgataattt	acttgttagtc	tttttatgatt	1500
acaccaatgt	attctagaaa	tagttatgtc	ttaggaaatt	gtggtttaat	tttgacttt	1560
ttacaggtaa	gtgccaagga	gaagtggttc	ctgaaatgtt	ctaatgttta	ttaacatttt	1620
aacccctcagc	tccatcagaa	tggaccgagt	ttagtaatca	ggaggataac	tatatgatct	1680
gaatggtata	ctaattggag	ctaaagacgc	ttttcaccag	ttgtttattt	gttggccgtg	1740
caaaaagattt	gttttcaaata	ggaaaacggg	cgaattcggt	ggacgctgtg	cagtttgg	1800
tccctgagaa	gatgggggggt	ttaaaagagg	aaaaaaaaaa	aggg		1844

<210> 33  
<211> 242  
<212> DNA  
<213> Homo sapien

<400> 33	gctctcactg	cctgtgagag	ccccatcg	gtgggtgtga	gtggcaggag	gtctcctctg	60
	ttcctcacaa	atttccggga	agccccaaatc	agagctgg	aaatagttgt	ttttaaagtt	120
	gaaggacgag	acattccaaat	agttcacaga	gtaatcaaag	ttcatgaaaa	agataatgga	180
	gacatcaaata	ttctgactaa	aggagataat	aatgaagtt	atgatagagg	cttgcataaa	240
	ga						242

<210> 34  
<211> 966  
<212> DNA  
<213> Homo sapien

<400> 34	aaggatcctt	aattaaat	atcccccc	ccccggc	cgtctgtgcc	acccagagcc	60
	ggcgccgc	taggtcccc	gagacc	ctgc	tatgg	gcgt	120
	tctcccc	tcgg	atatctt	cg	gg	ggggctca	
	ctattaccag	gttttaact	tcgccc	atg	gtt	tctct	180
	cttgc	atg	atc	gtt	gc	actcat	240
	ctcacaggca	gtgagagccc	catcg	gtt	gt	gtatg	300
	gccggcctt	cacagaggag	ac	cctgtt	c	catgaaagg	360
	agctgg	atagtttt	ttaa	agg	ttt	atgtt	420
	aatcaaagtt	catgaaaaa	ataatgg	gaga	at	caat	480
	tgaagttgat	gatagagg	gttaca	agg	ccaga	ac	540
	gg	gaga	tttaccata	ttt	ggat	gtat	600
	ctatccaaa	ttcaagtat	ctcttt	tttgc	tttgc	tttgc	660

tgaatcctaa aatgagaagc agttcctggg accagattga aatgaattct gttaaaaaag 720  
agaaaaacta atatatattga gatgttccat tttctgtata aaaggaaaca gtgtggaaat 780  
tgtccgcggc cttgggccaa gtaatagatt tgccgcgggg aaggaaatgg gagtttgta 840  
taaagatggt gcggcagctt ggaggctgtg ctgttccctt cgagttgggg ccgaataatc 900  
gaccatgtgt gcccttcctc gcgtccttct agctatgcgg gcgctatgaa ccgggcggtt 960  
gggttt 966

<210> 35  
<211> 717  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (685)..(686)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (688)..(688)  
<223> n=a, c, g, or t

<220>  
<221> misc\_feature  
<222> (697)..(697)  
<223> n=a, c, g, or t

<400> 35  
catgacacccg ggcacccagt ctcccttctt cctgctgtg ctccctcacag tgcttacagt 60  
tgttacaggt tctggtcatg caagctctac cccaggtgga gaaaaggaga ctccggctac 120  
ccagagaagt tcagtgccca gctctactga gaagaatgct tttaattcct ctctggaaga 180  
tcccagcacc gactactacc aagagctgca gagagacatt tctgaaatgg ctgtctgtca 240  
gtgccgcccga aagaactacg ggcagctgga catctttcca gccccggat acctaccatc 300  
ctatgagcga gtacccacc taccacaccc atgggcgcta tgtgccccct agcagtaccg 360  
atcgttagccc ctatgagaag gtttctgcag gtaatggtgg cagcagccctc tcttacacaa 420  
acccagcagt ggcagccact tctgccaact tgtaggggca cgtcgccccgc tgagctgagt 480  
ggccagccag tgccattcca ctccactcag gttcttcagg gccagagccc ctgcacctgt 540  
ttgggctgggt gagctgggag ttcaggtgg ctgctcacag cctccctcag aggccccacc 600  
aatttctcggt acacttctca gtgtgtggaa gctcatgtgg gcccctgagg gctcatgcct 660  
ggaaagtgtt gtgggtgggtg ctacnnanga ggactgnccc agagagccct gagatag 717

<210> 36  
<211> 774  
<212> DNA  
<213> Homo sapien

<400> 36  
catgacaccg ggcacccagt ctccttctt cctgctgctg ctcctcacag tgcttacagt 60  
tgttacaggt tctggtcatg caagctctac cccaggtgga gaaaaggaga cttcggctac 120  
ccagagaagt tcagtgccca gctctactga gaagaatgct tttaattcct ctctggaaga 180  
tcccagcacc gactactacc aagagctgca gagagacatt tctgaaatgg ctgtctgtca 240  
gtgccgcccga aagaactacg ggcagctgga catctttcca gccccgggat acctaccatc 300  
ctatgagcga gtaccccccacc taccacaccc atgggcgcta tgtgccccct agcagtaccc 360  
atcgtagccc ctatgagaag gttctgcag gtaatggtgg cagcagcctc tcttacacaa 420  
acccagcagt ggcagccact tctgccaact tgtagggca cgtcgccccgc tgagctgagt 480  
ggccagccag tgccattcca ctccactcag gttcttcagg gccagagccc ctgcaccctg 540  
tttgggctgg tgagctggga gttcaggtgg gctgctcaca gcctccttca gaggccccac 600  
caatttctcg gacacttctc agtgtgtgga agctcatgtg ggcccctgag ggctcatgcc 660  
tgggaagtgt tgtggtggt gctcccagga ggactggccc agagagccct gagatagcgg 720  
ggatcctgaa ctggactgaa taaaacgtgg tctccccctg cgccaaaaaa aaaa 774

<210> 37  
<211> 4144  
<212> DNA  
<213> Homo sapien

<400> 37  
ccgctccacc tctcaagaat tccctggctg cttgaatctg ttctgcccc tccccaccca 60  
tttcaccacc accatgacac cgggcaccca gtctccttc ttctctgtgc tgctcctcac 120  
agtgcttaca gttgttacag gttctggta tgcaagctct accccaggtg gaaaaagga 180  
gacttcggct acccagagaa gttcagtgcc cagctctact gagaagaatg ctgtgagtt 240  
gaccagcagc gtactctcca gccacagccc cggttcaggc tcctccacca ctcagggaca 300  
ggatgtcaact ctggccccgg ccacggAACC agcttcaggt tcagctgcca cctgggaca 360  
ggatgtcacc tcggtcccag tcaccaggcc agccctggc tccaccaccc cgccagccc 420  
cgatgtcacc tcagccccgg acaacaagcc agccccggc tccaccgccc ccccagccc 480  
cggtgtcacc tcggccccgg acaccaggcc ggccccggc tccaccgccc ccccagccc 540  
cggtgtcacc tcggccccgg acaccaggcc ggccccggc tccaccgcca gcccacggtg 600  
tcacctcgcc cccggacacc aggccgscac cgggctccac cgcccccscac gcccacggtg 660

tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	720
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	780
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	840
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	900
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	960
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1020
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1080
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1140
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1200
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1260
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1320
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1380
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1440
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1500
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1560
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1620
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1680
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1740
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1800
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1860
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1920
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	1980
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2040
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2100
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2160
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2220
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2280
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2340
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2400
tcacctcggc cccggacacc aggccggccc cgggctccac cgccccccca gcccacggtg	2460

tcacacctggc cccggacacc agggcgcccc cgggctccac cgccccccca gcccacggtg	2520
tcacacctggc cccggacacc agggcgcccc cgggctccac cgccccccca gcccacggtg	2580
tcacacctggc cccggacacc agggcgcccc cgggctccac cgccccccca gcccacggtg	2640
tcacacctggc cccggacacc agggcgcccc cgggctccac cgccccccca gcccacggtg	2700
tcacacctggc cccggacacc agggcgcccc cgggctccac cgccccccca gcccacggtg	2760
tcacacctggc cccggactcc aggtcggtct cgggcttctt accggccgccc gcagcccacg	2820
gtgtcacctc ggccccggac accaggccgg ccccggtctc caccggccccc ccagcccatg	2880
gtgtcacctc ggccccggac aacaggcccg cttggcgct ccaccggcccc tccagtccac	2940
aatgtcacct cggacctcagg ctctgcataa ggctcagctt ctactcttgt gcacaacggc	3000
acctctgccca gggctaccac aaccccgagcc agcaagagca ctccattctc aattcccagc	3060
caccactctg atactccctac cacccttgcc agccatagca ccaagactga tgccagtagc	3120
actcaccata gcacggtaacc tcctctcacc tcctccaatc acagcacttc tccccagttg	3180
tctactgggg tctctttctt ttccctgtct ttccacattt caaacctcca gttaattcc	3240
tctctggaag atcccagcac cgactactac caagagctgc agagagacat ttctgaaatg	3300
tttttgcaga ttataaaaca agggggtttt ctgggcctct ccaatattaa gttcaggccca	3360
ggatctgtgg tggtaacaatt gactctggcc ttccgagaag gtaccatcaa tgtccacgac	3420
gtggagacac agttcaatca gtataaaacg gaagcagctt ctcgatataa cctgacgatc	3480
tcagacgtca gcgtgagtgta tgtgccattt ctttctctg cccagtctgg ggctgggttg	3540
ccaggctggg gcatcgcgt gctggtgctg gtctgtgttc tgggtgcgt ggccattgtc	3600
tatctcatttgc cttggctgt ctgtcagtgc cgccgaaaga actacgggca gctggacatc	3660
tttccagccc gggataccta ccattctatg agcgagtacc ccacctacca cacccatggg	3720
cgctatgtgc cccctagcag taccgatctg agcccctatg agaaggtttc tgcaggtat	3780
ggtggcagca gcctctctta cacaacccca gcagtggcag ccacttctgc caactttag	3840
gggcacgtcg cccgctgagc tgagtggcca gccagtgcctt ccacttctgc caactttag	3900
tcagggccag agcccctgca ccctgtttgg gctggtgagc tggagttca ggtggcgtgc	3960
tcacagcctc ttccatggc cccaccaatt tctggacac ttctcagtgt gtggaaagtc	4020
atgtggccc ctgaggctca tgcctggaa gtgttgtgg ggctcccagg aggactggcc	4080
cagagagccc tgagatagcg gggatctga actggactga ataaaacgtg gtctccact	4140
gcga	4144

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<400> 38  
ccgctccacc tctcaagaat tccctggctg cttgaatctg ttctgcccc tccccaccca 60  
tttcaccacc accatgacac cgggcaccca gtctccttgc ttccctgctgc tgctcctcac 120  
agtgttaca gttgttacag gttctggta tgcaagctct accccaggtg gagaaaaggaa 180  
gacttcggct acccagagaa gttcagtgcc cagctctact gagaagaatg ctgtgagtat 240  
gaccagcagc gtactctcca gccacagccc cggttcaggg tcctccacca ctcagggaca 300  
ggatgtcact ctggccccgg ccacggaacc agcttcaggt tcagctgccca cctggggaca 360  
ggatgtcacc tcgggtccccag tcaccaggcc agccctgggc tccaccaccc cgccagccc 420  
cgatgtcacc tcagccccgg acaacaagcc agccccgggc tccaccggccc ccccagccc 480  
cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccggccc ccccagccc 540  
cggtgtcacc tcggccccgg acaccaggcc gsccccgggc tccaccggcsc ccscagccc 600  
cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccggccc ccccagccc 660  
ygggtgtcacc tcggccccgg acaacaggcc cgccattggcg ctccaccggcc cctccagtcc 720  
acaatgtcac ctggccctca ggctctgcat caggctcagc ttctactctg gtgcacaacg 780  
gcacccctgc cagggctacc acaacccag ccagcaagag cactccattc tcaattccca 840  
gccaccactc tgatactctt accacccttg ccagccatag caccaagact gatgccagta 900  
gcactcacca tagcacggta cctccctctca cctccctccaa tcacagcact tctccccagt 960  
tgtctactgg ggtctcttgc tttttctgt cttttcacat ttcaaaccctc cagtttaatt 1020  
cctctctgga agatcccagc accgactact accaagagct gcagagagac atttctgaaa 1080  
tggtgagtagt cggccttcc ttccccatgc tcccctgaag cagccatcag aactgtccac 1140  
acccttgca tcaaggctga gtccttccc tctcacccttca gttttgcag atttataaac 1200  
aagggggttt tctgggcctc tccaatatta agttcaggtt cagttctggg tgtggaccca 1260  
gtgtgggtgt tggagggttg ggtgggtgtc atgaccgttag gagggactgg tcgcacttaa 1320  
ggttggggga agagtcgtga gccagagctg ggaccctgtgg ctgaagtgcc catttccctg 1380  
tgaccaggcc aggatctgtg gtggtacaat tgactctggc ctcccgagaa ggtaccatca 1440  
atgtccacga cgtggagaca cagttcaatc agtataaaac ggaaggcagcc tctcgatata 1500  
acctgacgtat ctcagacgtc agccgtgagg ctactccct ggctgcagcc cagcaccatca 1560  
ccggggccct ctcctccatc tgccctgggtc cccgctctt ccttagtgct ggcagcggga 1620  
ggggcgcctc ctctgggaga ctgccttgac cactgctttt ccttttagtg agtgatgtgc 1680  
catttccctt ctctgcccag tctggggctg gggtgccagg ctggggcatac gcgctgctgg 1740

tgctggtctg tgttctggtt gcgcgtggcca ttgtctatct cattgccttg gtgagtgcag 1800  
tccctggccc tgatcagagc cccccggtag aaggcactcc atggcctgccc ataacctcct 1860  
atctccccag gctgtctgtc agtgcgcggc aaagaactac gggcagctgg acatcttcc 1920  
agcccgggat acctaccatc ctatgagcga gtaccccacc taccacaccc atgggcgccta 1980  
tgtgccccct agcagtaccg atcgtagccc ctatgagaag gtgagattgg ccccacaggc 2040  
caggggaagc agagggtttg gctggcaag gattctgaag ggggtacttg gaaaacccaa 2100  
agagcttgga agaggtgaga agtggcgtga agtgagcagg ggagggcctg gaaaggatga 2160  
ggggcagagg tcagaggagt tttggggac aggctggga ggagactatg gaagaaaggg 2220  
gccctcaaaa gggagtggcc ccactgccag aattc 2255

<210> 39  
<211> 1953  
<212> DNA  
<213> Homo sapien

<400> 39  
ccgctccacc tctcaagaat tccctggctg cttaaatctg ttctgcccccc tccccaccca 60  
tttcaccacc accatgacac cgggcaccca gtctccttcc ttctgtctgc tgctcctcac 120  
agtgttaca gctaccacag cccctacacc cgcaacagtt gttacaggtt ctggtcatgc 180  
aagcttacc ccaggtggag aaaaggagac ttctggctacc cagagaagtt cagtgcccg 240  
ctctactgag aagaatgctg tgagtatgac cagcagcgta ctctccagcc acagccccgg 300  
ttcaggctcc tccaccactc agggacagga tgtcactctg gccccggcca cggaaccagc 360  
ttcaggttca gctgccacct gggacagga tgtcacctcg gtcccagtca ccaggccagc 420  
cctgggctcc accaccccgcc cagcccacga tgtcacctca gccccggaca acaagccagc 480  
ccccggctcc accgcccccc cagcccacgg tgtcacctcg gccccggaca ccaggccggc 540  
ccccggctcc accgcccccc cagcccacgg tgtcacctcg gccccggaca ccaggccggc 600  
ccccggctcc accgcccccc cagcccatgg tgtcacctcg gccccggaca acaggcccg 660  
cttggcgctc caccccccct ccagtccaca atgtcacctc ggctcagggc tctgcatcg 720  
gctcagcttc tactctggtg cacaacggca cctctgcccag ggctaccaca accccagcc 780  
gcaagagcac tccatttca attcccgcc accactctga tactcctacc acccttggca 840  
gccatagcac caagactgat gccagtagca ctcaccatag cacggtaccc cctctcacct 900  
cctccaatca cagcacttct ccccgatgtgt ctactgggt ctctttttt ttctgttctt 960  
ttcacatttc aaacctccag tttaattccct ctctggaaga tcccagcacc gactactacc 1020  
ttcacatttc aaacctccag tttaattccct ctctggaaga tcccagcacc gactactacc 1080

aagagctgca gagagacatt tctgaaatgt ttttgcagat ttataaaacaa gggggtttc	1140
tgggcctctc caatattaag ttcaggccag gatctgtggt ggtacaattt actctggct	1200
tccgagaagg taccatcaat gtccacgacg tggagacaca gttcaatcag tataaaaacgg	1260
aagcagcctc tcgatataac ctgacgatct cagacgtcag cgtgagtgtat gtgccatttc	1320
ctttctctgc ccagtctggg gctggggtgc caggctgggg catcgcgctg ctgggtctgg	1380
tctgtgttct ggttgcgcgtg gccattgtct atctcattgc cttggctgtc tgtcagtgcc	1440
gccgaaagaa ctacgggcag ctggacatct ttccagcccg ggataacctac catcctatga	1500
gcgagtaccc cacctaccac acccatgggc gctatgtgcc ccctagcagt accgatcgta	1560
gccctatga gaaggtttct gcaggtaatg gtggcagcag cctctttac acaaaccagg	1620
cagtggcagc cacttctgcc aacttgttagg ggcacgtcgc ccgtgagct gagtggccag	1680
ccagtgccat tccactccac tcaggttctt cagggccaga gcccctgcac cctgtttggg	1740
ctggtgagct gggagttcag gtgggctgtcacagcctcc ttcagaggcc ccaccaattt	1800
ctcgacact tctcagtgtg tggaagctca tgtggggcccc tgaggctcat gcctgggaag	1860
tgttgtgggg gctcccagga ggactggccc agagagccct gagatagcgg ggatcctgaa	1920
ctggactgaa taaaacgtgg tctccactg cga	1953

<210> 40  
<211> 1738  
<212> DNA  
<213> Homo sapien

<400> 40	
ccgctccacc tctcaagaat tccctggctg cttgaatctg ttctgcccccc tccccaccca	60
tttaccacc accatgacac cgggcaccca gtctccttcc ttctgctgc tgctcctcac	120
agtgttaca gttgttacag gttctggta tgcaagctct accccaggtg gagaaaagga	180
gacttcggct acccagagaa gttcagtgtcc cagctctact gagaagaatg ctgtgagtat	240
gaccagcagc gtactctcca gccacagccc cggttcaggc tcctccacca ctcaggacca	300
ggatgtcaact ctggccccgg ccacggAACCC agttcaggt tcagctgcca cctggggaca	360
ggatgtcacc tcggtccccag tcaccaggcc agccctgggc tccaccaccc cgccagccca	420
cgtgtcacc tcagccccgg acaacaagcc agccccgggc tccaccggccc ccccaagccca	480
cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccggccc ccccaagccca	540
cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccggccc ccccaagccca	600
tgggtgtcacc tcggccccgg acaacaggcc cgcccttggcg ctccaccggcc cctccagtcc	660
	720

acaatgtcac	ctcgccctca	ggctctgcat	caggctcagc	ttctactctg	gtgcacaacg	780
gcacctctgc	cagggctacc	acaaccccag	ccagcaagag	cactccattc	tcaattccca	840
gccaccactc	tgatactcct	accacccttg	ccagccatag	caccaagact	gatgccagta	900
gcactcacca	tagcacggta	cctcctctca	cctcctccaa	tcacagcact	tctccccagt	960
tgtctactgg	ggtctcttgc	tttttctgt	cttttcacat	ttcaaaccctc	cagtttaatt	1020
cctctctgga	agatcccagc	accgactact	accaagagct	gcagagagac	atttctgaaa	1080
tgttttgca	gatttataaa	caagggggtt	ttctgggct	ctccaatatt	aagttcaggc	1140
caggatctgt	ggtggtacaa	ttgactctgg	ccttccgaga	aggtaccatc	aatgtccacg	1200
acgtggagac	acagttcaat	cagtataaaa	cggaagcagc	ctctcgatat	aacctgacga	1260
tctcagacgt	cagcgtgagt	gatgtccat	ttccttctc	tgcccaagtct	ggggctgggg	1320
tgccaggctg	gggcattcgcg	ctgctggcgc	tggctgtgt	tctggttgcg	ctggccattg	1380
tctatctcat	tgccttggt	gtctgtcagt	gccgcccggaa	gaactacggg	cagctggaca	1440
tctttccagc	ccgggatacc	taccatccta	tgagcgagta	ccccacctac	cacacccatg	1500
ggcgctatgt	gcccccttagc	agtaccgatc	gtagccctta	tgagaagggtt	tctgcaggtt	1560
atggtggcag	cagcctctct	tacacaaacc	cagcagtgcc	agccacttct	gccaacttgt	1620
aggggcacgt	cgcccgtga	gctgagtgcc	cagccagtgcc	cattccactc	cactcaggcc	1680
tctctggcc	agtccctctg	ggagccccc	ccacaacact	tcccaggcat	ggaattcc	1738

<210> 41  
<211> 328  
<212> DNA  
<213> Homo sapien

<400> 41	tcatctcgag	cgccggcgca	gtgtgaggcg	gccccggctc	accgcgcccc	cagcccacgg	60
	tgtcacctcg	gccccggaca	ccaggccggc	cccgggctcc	accgcgcccc	cagcccacgg	120
	tgtcacctcg	gccccggaca	ccaggccggc	cccgggctcc	accgcggcccc	cagcccatgg	180
	tgtcaccttc	gtgccyccga	cctcaggtcg	gcgccttgct	ctctttctgg	tctatgtgtt	240
	ccgtgttagta	agatgttagtt	cagacgcgtc	tcgatacact	acgatagcg	aagtataatcg	300
	atggatcata	cgtgtttcc	gtgtgtga				328

<210> 42  
<211> 1030  
<212> DNA  
<213> Homo sapien

<220>

<221> misc\_feature  
<222> (574)..(574)  
<223> n=a, c, g, or t

<400> 42		
ccgctccacc tctcaagaat tccctggctg cttgaatctg ttctgcccccc tccccaccca	60	
tttcaccacc accatgacac cgggcaccca gtctccttgc ttccctgctgc tgctcctcac	120	
agtgtttaca gttaccacag cccctacacc cgcaacagtt gttacagggtt ctggcatgc	180	
aagctctacc ccaggtggag aaaaggagac ttccggctacc cagagaagtt cagtggccag	240	
ctctactgag aagaatgctg ttagtatgac cagcagcgta ctctccagcc acagccccgg	300	
ttcaggctcc tccaccactc agggacagga tgtcaactctg gccccggcca cggaaaccagc	360	
ttcaggttca gtcgccacctt ggggacagga tgcacccctcg gtcccagtca ccaggccagc	420	
cctgggctcc accacccccc cagcccacga tgcacccctca gccccggaca acaagccagc	480	
cccggttca gctgtttcta gtaggtgctc accntacgca gttactaact tacgactgag	540	
cgtgtcgct ttgcactaga cgatcgtaa ctggaaacac ctcatgtgct gtcatacaa	600	
tttattcgct ttgcggcgcg atccccctgt tcgcaagagg gtggaaagagg ccactgttg	660	
taccccgcga acttagatcg tcggcggtgc tagactagat cacccctttg cgcagagact	720	
gagagtattg gggacccaga aaacagaagc tgggggttca ggagtttgc acgacaaaaga	780	
actacgatag cagaagactt gatggtactg gtgacccaag gagaaatctg gggattttaga	840	
ggccacctga aagatacgaa gatacaaata cagtctgaga tgctggggac ccaggagaca	900	
gaggtggaca gcttctaggg taccagagtc agaggctgag ggggacagaa cgctaaaata	960	
tttagggaccc	1020	
	1030	

<210> 43  
<211> 1918  
<212> DNA  
<213> Homo sapien

<400> 43		
taggaggttag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg	60	
gcggggcgccc ggggagtggg gggaccggta taaagcggta ggccctgtgc cccgctccac	120	
ctctcaagca gccagcgct gcctgaatct gttctgcccccc ctccccaccc atttcaccac	180	
caccatgaca cccggcacccc agtctccttt ctccctgctg ctgctcctca cagtgtttac	240	
agttgttaca ggttctggtc atgcaagctc taccctagggt ggagaaaagg agacttcggc	300	
tacccagaga agttcagtgc ccagctctac tgagaagaat gctgtgagta tgaccagcag	360	

42

cgtactctcc agccacagcc ccggttcagg ctccctccacc actcagggac aggatgtcac 420  
tctggccccg gccacggaac cagttcagg tttagctgcc acctggggac aggatgtcac 480  
ctcggtccca gtcaccaggc cagccctggg ctccaccacc ccggccagccc acgtatgtcac 540  
ctcagccccg gacaacaaggc cagccccggg ctccaccggc ccccccagccc acggtgtcac 600  
ctcgcccccg gacaccaggc cggcccccggg ctccaccggc ccccccagccc atggtgtcac 660  
ctcgcccccg gacaacaggc ccgccttggg ctccaccggc cctccagttcc acaatgtcac 720  
ctcgccctca ggctctgtcat caggctcage ttctactctg gtgcacaacg gcacctctgc 780  
cagggttacc acaaccccg ccagcaagag cactccattc tcaattccca gccaccactc 840  
tgatactctt accaccotttgc ccagccatag caccaagact gatgccagta gcactcacca 900  
tagcacggta cctccctctca cctccctccaa tcacagcaact tctccccagt tgtctactgg 960  
ggtctctttc ttttccctgt cttttcacat ttcaaaacctc cagtttaatt cctctctgg 1020  
agatcccagc accgactact accaagagct gcagagagac atttctgaaa tgttttgca 1080  
gatttataaa caagggggtt ttctgggcct ctccaatatt aagttcaggc caggatctgt 1140  
ggtggtacaa ttgactctgg cttccgaga aggtaccatc aatgtccacg acgtggagac 1200  
acagttcaat cagtataaaa cggaagcagc ctctcgatata aacctgacga tctcagacgt 1260  
cagcgtgagt gatgtgcatt ttcccttctc tgcccgatct ggggctgggg tgccaggctg 1320  
gggcattcgcg ctgctggtgc tggctgtgt tctgggtgcg ctggccattt tctatctcat 1380  
tgccttggct gtctgtcagt gcccggaaaa gaactacggg cagctggaca tctttccagc 1440  
ccgggataacc taccatccta tgagcgagta ccccacctac cacacccatg ggcgctatgt 1500  
gcccccttagc agtaccgatc gtggccctta tgagaagggt tctgcaggta atgggtggcag 1560  
cagccctctt tacacaaacc cagcagtggc agccacttct gccaacttgt aggggcacgt 1620  
cgccccctga gctgagtggc cagccagtgc cattccactc cactcagggtt ctccaggggcc 1680  
agagccccctg caccctgttt gggctggta gctggggagtt caggtgggct gctcacagcc 1740  
tccttcagag gccccaccaa tttctcgac acttctcagt gtgtggaaac tcattgtggc 1800  
ccctgaggggc tcattgcctgg gaagtgttgtt ggtgggggct cccaggagga ctggcccaga 1860  
gagccctgag atagcgggaa tcctgaaactg gactgaataa aacgtggtct cccactgc 1918

<210> 44  
<211> 1755  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1682)..(1682)

<223> n=a, c, g, or t

<220>

<221> misc\_feature

<222> (1733)..(1733)

<223> n=a, c, g, or t

<400> 44

taggaggtag	gggagggggc	ggggtttgt	cacctgtcac	ctgctccggc	tgtgctatgg	60
gcggggcgggc	ggggagtggg	gggacccgta	taaagcgta	ggcgccctgtg	cccgctccac	120
ctctcaagca	gccagcgct	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
caccatgaca	ccgggcaccc	agtctcttt	cttctgtcg	ctgctcctca	cagtgcttac	240
agttgttaca	ggttctgtc	atgcaagctc	taccccagg	ggagaaaagg	agacttcggc	300
tacccagaga	agttcagtgc	ccagctctac	tgagaagaat	gctgtgagta	tgaccagcag	360
cgtactctcc	agccacagcc	ccgggttcagg	ctccctccacc	actcagggac	aggatgtcac	420
tctggccccc	gccacggAAC	cagcttcagg	ttcagctgcc	acctggggac	aggatgtcac	480
ctcggtccca	gtcaccaggc	cagccctggg	ctccaccacc	ccgcccagccc	acgatgtcac	540
ctcagccccc	gacaacaaggc	cagccccggg	ctccaccgcc	cccccagccc	acggtgtcac	600
ctcggtcccg	gacaccaggc	cggcccccggg	ctccaccgcc	cccccagccc	atggtgtcac	660
ctcggtcccg	gacaacaggc	cgccttggg	ctccaccgcc	cetccagtcc	acaatgtcac	720
ctcggtccca	ggctctgcat	caggtcagc	ttctactctg	gtgcacaacg	gcacctctgc	780
cagggctacc	acaacccag	ccagcaagag	cactccattc	tcaattccca	gccaccactc	840
tgatactcct	accacccctg	ccagccatag	caccaagact	gatgccagta	gcactcacca	900
tagcacggta	cctcctctca	cctcctccaa	tcacagcact	tctcccaagt	tgtctactgg	960
ggtctcttcc	ttttcctgt	ctttcacat	ttcaaaccctc	cagtttaatt	cctctctgga	1020
agatcccagc	accgactact	accaagagct	gcagagagac	atttctgaaa	tgttttgca	1080
gatttataaa	caagggggtt	ttctgggcct	ctccaatatt	aagttcaggc	caggatctgt	1140
ggtgttacaa	ttgactctgg	ccttccgaga	aggtaccatc	aatgtccacg	acgtggagac	1200
acagttcaat	cagtataaaa	cggaagcagc	ctctcgatat	aacctgacga	tctcagacgt	1260
cagcgtgagt	gatgtgccat	ttcccttctc	tgcccagtct	ggggctgggg	tgccaggctg	1320
gggcacatcgcg	ctgctggtgc	tggctgtgt	tctggttgcg	ctggccattg	tctatctcat	1380
tgccttggct	gtctgtcagt	gccgccgaaa	gaactacggg	cagctggaca	tctttccagc	1440
ccgggatacc	taccatccta	tgagcgagta	ccccacccatc	cacacccatg	ggcgctatgt	1500
ccccccctagc	agtaccgatc	gtagccctta	tgagaagg	tctgcaggta	atggtgtggcag	1560

cagcctctct tacacaaacc cagcagtggc agccacttct gccaacttgt aggggcacgt 1620  
cgccccgctga gctgagtggc cagccagtgc cattccactc cactcaggtt cttcaggcag 1680  
ancctgacct gttggctgta gctggagtca gtggtgtaag ctcttcaagg ggncagtc 1740  
cgatatgtaa cgttc 1755

<210> 45  
<211> 1530  
<212> DNA  
<213> Homo sapien

<400> 45  
taggaggttag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcggggcgggc ggggagtggg gggaccggta taaagcggta ggcgcctgtg cccgctccac 120  
ctctcaagca gccagcgcct gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca ccgggcaccc agtctcctt cttectgctg ctgctcctca cagtgc 240  
atttgcatac ggttctggtc atgcaagctc taccccaggt ggagaaaagg agacttcggc 300  
tacccagaga agttcagtgc ccagctctac tgagaagaat gcttttaatt cctctctgga 360  
agatcccagc accgactact accaagagct gcagagagac atttctgaaa tgttttgca 420  
gatttataaa caagggggtt ttctggcct ctccaatatt aagttcaggc caggatctgt 480  
ggtgttacaa ttgactctgg cttccgaga aggtaccatc aatgtccacg acgtggagac 540  
acagttcaat cagtataaaa cggaaagcgc ctctcgatata aacctgacga tctcagacgt 600  
cagcgtgagt gatgtgccat ttcccttctc tgcccagtct gggctgggg tgccaggctg 660  
gggcattcgcg ctgctgggtc tggctgtgt tctggttcg 840  
tgccctggct gtctgtcagt gcccggaaa gaactacggg cagctggaca tcttccagc 720  
ccgggataacc taccatccta tgagcgagta ccccacctac cacacccatg ggcgc 780  
gccccctagc agtaccgatc gtagcccta tgagaagg 900  
cagcctctct tacacaaacc cagcagtggc agccacttct gccaacttgt aggggcacgt 960  
cgccccgctga gctgagtggc cagccagtgc cattccactc cactcaggtt ctccaggc 1020  
agagccccctg caccctgttt gggctggta gctggagtt caggtgggt gctcacagcc 1080  
tccttcagag gccccacgac tatttcagga agttcgaacc ccacctgtac tccctcgact 1140  
ccaaacagcga ccatgtggac tctctgacag acgaggagat cctgtccaa 1200  
gcatgctgca cttagcact cagtagcacc tgctgcacaa ccacccatc gtgcgcgtga 1260  
tcgaggccag ggacctgcca cctccatct cccacgtgg ctgcgcgcag gacatggc 1320  
actccaaacc ctagtcaag atctgtctcc tgccagacca gaagaactca aagcagacccg 1380

gggtcaaacg caagaccagg aagcccggtt ttgaggagcg ctacacccctc gagatcccc 1440  
tcctggaggc ccagaggagg accctgtcc tgaccgttgt ggattttgat aagttctccc 1500  
gccactgtgt cattggaaa gtttctgtgg 1530

<210> 46  
<211> 563  
<212> DNA  
<213> Homo sapien

<400> 46  
ttttgtttt ttgcacccag aggcaaaatg ggtggagcac tatgcccagg ggagcccttc 60  
ccgaggagtc ccaggggtga gcctctgtgc ccctaattcat ctccttagaa tggagggttag 120  
accgagaaag gctggcatag ggggagggtt cccaggtaga agaagaagtgc tcagcagacc 180  
aggtttctgc aggttaatggt ggcagcagcc tctcttacac aaacccagca gtggcagcca 240  
cttctgccaa cttgttagggg cacgtcgccc gctgagctga gtggccagcc agtgcattc 300  
cactccactc aggttcttca gggccagagc ccctgcaccc tggggggct ggtgagctgg 360  
gagttcaggt gggctgctca cagcctcattt cagaggcccc accaatttct cggacacttc 420  
tcagtgtgtg gaagctcatg tggggccctg agggctcatg cctggaaagt gttgtggtgg 480  
gggctccag gaggactggc ccagagagcc ctgagatagc gggatcctg aactggactg 540  
aataaaacgt ggtctccac tgc 563

<210> 47  
<211> 1945  
<212> DNA  
<213> Homo sapien

<400> 47  
taggaggttag gggagggggc ggggttttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcggggcgccc ggggagtggtt gggaccggta taaagcggtt ggcgcctgtg cccgctccac 120  
ctctcaagca gccagcgcct gctgaatct gttctgcctt ctccttaccc atttcaccac 180  
caccatgaca cccggccaccc agtctccctt cttctgtgt ctgctctca cagtgtttac 240  
agctaccaca gcccctaaac ccgcaacagt ttttacaggt tctggtcatg caagctctac 300  
cccaggtgga gaaaaggaga cttcggtac ccagagaagt tcagtgcctt gctctactga 360  
gaagaatgct gtgagtgatga ccagcagcgt actctccagc cacagccccg gttcaggctc 420  
ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag cttcagggttc 480  
agctgccacc tggggacagg atgtcacctc ggtccctgtc accaggccag ccctggctc 540  
caccaccccg ccagccacg atgtcacctc agccccggac aacaagccag ccccggttc 600

caccggcccc	ccagccccacg	gtgtcacctc	ggcccccggac	accaggccgg	ccccgggctc	660
caccggcccc	ccagccccatg	gtgtcacctc	ggcccccggac	aacaggcccc	ccttgggctc	720
caccggcccc	ccagtcacaca	atgtcacctc	ggcctcaggc	tctgcatcag	gctcagcttc	780
tactctggtg	cacaacggca	cctctgccag	ggctaccaca	accccagcca	gcaagagcac	840
tccattctca	atccccagcc	accactctga	tactcctacc	acccttgcca	gccatagcac	900
caagactgat	gccagtagca	ctcaccatag	cacggtaacct	cctctcacct	cctccaatca	960
cagcacttct	ccccagttgt	ctactggggt	ctctttcttt	ttctgtctt	ttcacatttc	1020
aaacctccag	ttaattct	ctctggaaga	tcccagcacc	gactactacc	aagagctgca	1080
gagagacatt	tctgaaatgt	tttgcatgt	ttataaacaa	gggggtttc	tggccctctc	1140
caatattaag	ttcaggccag	gatctgtgg	ggtacaattg	actctggcct	tccgagaagg	1200
taccatcaat	gtccacgacg	tggagacaca	gttcaatcag	tataaaacgg	aaggcagcctc	1260
tcgatataac	ctgacgatct	cagacgtcag	cgtgagtgtat	gtgccatttc	ctttctctgc	1320
ccagtctggg	gctgggggtgc	caggctgggg	catcgcgctg	ctggtgctgg	tctgtgttct	1380
ggttgcgctg	gccattgtct	atctcattgc	cttggctgtc	tgtcagtgcc	gccgaaagaa	1440
ctacggcag	ctggacatct	ttccagcccc	ggataacctac	catcctatga	gcgagtaccc	1500
cacctaccac	acccatgggc	gctatgtgcc	ccctagcagt	accgatcgta	gcccctatga	1560
gaaggtttct	gcaggtaatg	gtggcagcag	cctcttttac	acaaaacccag	cagtggcagc	1620
cacttctgcc	aacttgttagg	ggcacgtcgc	cctgtgagct	gagtggccag	ccagtgccat	1680
tccactccac	tcaggttctt	cagggccaga	gcccctgcac	cctgtttggg	ctggtgagct	1740
gggagttcag	gtgggctgct	cacagcctcc	ttcagaggcc	ccaccaaattt	ctcggacact	1800
tctcagtgtg	tggaagctca	tgtggccccc	tgagggctca	tgcctggaa	gtgttgtgg	1860
gggggctccc	aggaggactg	gcccagagag	ccctgagata	gcggggatcc	tgaactggac	1920
tgaataaaac	gtggtctccc	actgc				1945

<210> 48  
<211> 1882  
<212> DNA  
<213> Homo sapien

<400> 48	taggaggtag	gggagggggc	ggggtttgt	cacctgtcac	ctgctccggc	tgtgctatgg	60
	gcgggggggc	ggggagtggg	gggaccggta	taaagcggt	ggccctgtg	cccgctccac	120
	ctctcaagca	gccagcgct	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctcctt	ttcctgtg	ctgctcctca	cagtgttac	240

aggtggagaa	aaggagactt	cggctaccca	gagaagtca	gtgcccagct	ctactgagaa	300
gaatgctgtg	agtatgacca	gcagcgtact	ctccagccac	agccccggtt	caggctcc	360
caccactcg	ggacaggatg	tcactctggc	cccgccacg	gaaccagtt	caggttcagc	420
tgcacacctgg	ggacaggatg	tcacctcggt	cccagtcacc	aggccagccc	tgggctccac	480
caccccgcca	gcccacgatg	tcacctcage	cccgacaaac	aagccagccc	cgggctccac	540
cgcggggcca	gcccacggtg	tcacctcgac	cccgacacc	aggccggccc	cgggctccac	600
cgcggggcca	gcccacatggt	tcacctcgac	cccgacaaac	aggccggccc	tgggctccac	660
cgcggggcca	gtccacaatg	tcacctcgac	ctcaggctct	gcatcaggct	cagcttctac	720
tctggtgcac	aacggcacct	ctgccagggc	taccacaacc	ccagccagca	agagcactcc	780
attctcaatt	cccagccacc	actctgatac	tcctaccacc	cttgcagcc	atagcaccaa	840
gactgatgcc	agtagcactc	accatagcac	ggtacctct	ctcacctct	ccaatcacag	900
cacttctccc	cagttgtcta	ctgggtctc	tttcttttc	ctgtctttc	acatttcaaa	960
cctccagttt	aattcctctc	tggaaagatcc	cagcaccgac	tactaccaag	agctgcagag	1020
agacatttct	gaaatgtttt	tgcagattta	taaacaaggg	ggtttctgg	gcctctccaa	1080
tattaagtcc	aggccaggat	ctgtggtggt	acaattgact	ctggccttcc	gagaaggta	1140
catcaatgtc	cacgacgtgg	agacacagtt	caatcagtt	aaaacggaag	cagcctctcg	1200
atataacctg	acgatctcag	acgtcagcgt	gagtgatgt	ccatttcctt	tctctgccc	1260
gtctgggct	gggggtgcag	gctggggcat	cgcgctgctg	gtgctggct	gtgttctgg	1320
tgcgctggcc	attgtctatc	tcattgcctt	ggctgtctgt	cagtgcgc	gaaagaacta	1380
cggcagctg	gacatcttc	cagccggga	tacctaccat	cctatgagcg	agtacccac	1440
ctaccacacc	catgggcgct	atgtcccc	tagcagtacc	gatcgtagcc	cctatgagaa	1500
ggtttctgca	ggtaatggtg	gcagcagcct	ctcttacaca	aacccagcag	tggcagccac	1560
ttctgccaac	ttgttagggc	acgtcgcccc	ctgagctgag	tggccagcca	gtgccattcc	1620
actccactca	ggttcttcag	ggccagagcc	cctgcaccc	gttgggctg	gtgagctgg	1680
agttcaggtg	ggctgctcac	agcctccttc	agaggcccc	ccaatttctc	ggacacttct	1740
cagtgtgtgg	aagctcatgt	ggggccctga	gggctcatgc	ctggaaagt	ttgtggtgg	1800
ggctcccagg	aggactggcc	cagagagccc	tgagatagcg	gggatcctga	actggactga	1860
ataaaacgtg	gtctcccact	gc				1882

<210> 49  
 <211> 1930  
 <212> DNA  
 <213> Homo sapien

<400> 49  
gtcgctctag aggaccctc ataggttcgc agggccatga gccaaaggcct atgggcagag 60  
agaaggaggg tgctgcaggg aaggaggcgg ccaaccagg gttactgag gctgccact 120  
ccccagtccct cctggtatta ttctctggt ggccagagct tatattttct tcttgcttt 180  
attttcctt cataaaagacc caaccctatg actttaactt ctacagcta ccacagcccc 240  
taaacccgca acagttgtta caggttctgg tcatgcaagc tctaccccag gtggagaaaa 300  
ggagacttcg gctaccaga gaagttagt gcccagctct actgagaaga atgctgttag 360  
tatgaccagc agcgtactct ccagccacag ccccggttca ggctcctcca ccactcaggg 420  
acaggatgtc actctggccc cgccacacgg accagcttca ggttcagctg ccacctgggg 480  
acaggatgtc acctcggtcc cagtcaccag gccagccctg ggctccacca ccccgccagc 540  
ccacgatgtc acctcagccc cggacaacaa gccagccccg ggctccacccg cccccccagc 600  
ccacgggtgtc acctcggtccc cggacacccag gccggccccg ggctccacccg cccccccagc 660  
ccatgggtgtc acctcggtccc cggacaacacag gcccgccttg ggctccacccg cccccccagc 720  
ccacaatgtc acctcggtct caggctctgc atcaggctca gcttctactc tggtgaccaa 780  
cggcacctct gccagggtcta ccacaacccc agccagcaag agcactccat tctcaattcc 840  
cagccaccac tctgataactc ctaccacccct tgccagccat agcaccaaga ctgatgccag 900  
tagcaactcac catagcacgg tacctcctct cacccctcc aatcacagca cttctccca 960  
gttgtctact ggggtctctt tcttttctt gtctttcac atttcaaacc tccagttaa 1020  
ttcctctctg gaagatccca gcaccgacta ctaccaagag ctgcagagag acatttctga 1080  
aatgtttttg cagattata aacaaggggg ttttctggc ctctccaata ttaagtttag 1140  
gccaggatct gtgggtggtag aattgactct ggccctccga gaaggtacca tcaatgtcca 1200  
cgacgtggag acacagttca atcagtataa aacggaagca gcctctcgat ataacctgac 1260  
gatctcagac gtcagcgtga gtgatgtgcc atttccttcc tctgcccagt ctggggctgg 1320  
ggtgccaggc tggggcatcg cgctgctggt gctggtctgt gttctgggttgcgctggccat 1380  
tgtctatctc attgccttgg ctgtctgtca gtgccgcccga aagaactacg ggcagctgg 1440  
catcttcca gcccggata cctaccatcc tatgagcggag taccacccaccc accacaccca 1500  
tgggcgtat gtgcccccta gcagtaccga tcgttagcccc tatgagaagg tttctgcagg 1560  
taatggtggc agcagcctct cttacacaaa cccagcagtgc gcagccactt ctgccaactt 1620  
gtaggggcac gtcgcccgtc gagctgagtg gccagccagt gccattccac tccactcagg 1680  
ttcttcaggg ccagagcccc tgcaccctgt ttgggctggt gagctggag ttcaggtgg 1740  
ctgctcacag ctccttcag aggccccacc aatttctcgg acacttctca gtgtgtggaa 1800

gctcatgtgg gcccctgagg gctcatgcct gggaaagtgtt gtgggtgggg ctcccaggag 1860  
gactggccca gagagccctg agatacgccc gatcctgaac tggactgaat aaaacgtgg 1920  
ctcccactgc 1930

<210> 50  
<211> 1798  
<212> DNA  
<213> Homo sapien

<400> 50  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcgggcgggc ggggagtggg gggaccggta taaagcggta ggccgcctgtg cccgctccac 120  
ctctcaagca gccagcgcct gcctgaatct gttctgcccc ctccccaccc attcaccac 180  
caccatgaca cccggcaccc agtctccctt cttcctgctg ctgctcctca cagtgcattac 240  
agttgttaca gggtctggtc atgcaagctc taccccaaggt ggagaaaagg agacttcggc 300  
tacccagaga agttcagtgcc ctagtctac tgagaagaat gctgtgagta tgaccagcag 360  
cgtactctcc agccacagcc ccgggttcagg ctccctccacc actcagggac aggatgtcac 420  
tctggccccc gccacggAAC cagtttcagg ttcaagctgcc acctggggac aggatgtcac 480  
ctcggtccca gtcaccaggc cagccctggg ctccaccacc ccggccagccc acgatgtcac 540  
ctcggtcccg gacaacaggc ccgccttggg ctccaccggc cctccagtcc acaatgtcac 600  
ctcggcctca ggctctgcat caggctcagc ttctactctg gtgcacaacg gcacctctgc 660  
cagggctacc acaacccag ccagcaagag cactccattc tcaattccca gccaccactc 720  
tgatactcct accacccttg ccagccatag caccaagact gatgccagta gcactcacca 780  
tagcacggta cctcctctca cctcctccaa tcacagcact tctcccaagt tgtctactgg 840  
ggtctcttc ttttccctgt ctttcacat ttcaaacctc cagtttaatt cctctctgg 900  
agatcccagc accgactact accaagagct gcagagagac atttctgaaa tgttttgca 960  
gatttataaa caagggggtt ttctgggcct ctccaatatt aagttcaggc caggatctgt 1020  
ggtgttacaa ttgactctgg cttccgaga aggtaccatc aatgtccacg acgtggagac 1080  
acagttcaat cagtataaaa cggaagcagc ctctcgatata aacctgacga tctcagacgt 1140  
cagcgtgagt gatgtgcacat ttctttctc tgcccagtct gggctgggg tgccaggctg 1200  
gggcatecgcg ctgctgggc tggctctgtgt tctgggtgc ctggccattg tctatctcat 1260  
tgccttggct gtctgtcagt gcccggaaa gaactacggg cagctggaca tctttccagc 1320  
ccgggataacc taccatccta tgagcggagta ccccacctac cacacccatg ggccgtatgt 1380  
gccccctagc agtaccgatc gtagccctta tgagaagggtt tctgcaggta atggtggcag 1440

cagcctctct tacacaaaacc cagcagtggc agccacttct gccaacttgt aggggcacgt	1500
cgcggcgctga gctgagtggtc cagccagtgc catccactc cactcagggtt ctccaggccc	1560
agagccccctg caccctgttt gggctgggtga gctgggagtt caggtgggtc gctcacagcc	1620
tccttcagag gccccaccaa tttctcggac acttctcagt gtgtggaaac tcatgtggc	1680
ccctgagggc tcatacgctgg gaagtgttgt ggtggggct cccaggagga ctggcccaga	1740
gagccctgag atagcgggga tcctgaactg gactgaataa aacgtggctc cccactgc	1798

<210> 51  
<211> 1312  
<212> DNA  
<213> Homo sapien

<400> 51	
taggaggttag gggagggggc ggggttttgt cacctgtcac ctgctccggc tgtgctatgg	60
gcggggcgggc ggggagtggtt gggaccggta taaagcggta ggccctgtg cccgctccac	120
ctctcaagca gccagcgccct gcctgaatct gttctgcccc ctccccaccc atttaccac	180
caccatgaca ccgggcaccc agtctccctt ctccctgctg ctgctcctca cagtgtttac	240
agttgttaca ggttctggtc atgcaagctc tacccaggt ggagaaaaagg agacttcggc	300
tacccagaga agttcagtgc ccagctctac tgagaagaat gctttgtcta ctggggtctc	360
tttcttttc ctgtcttttc acatttcaaa cctccagttt aattcccttc tggaagatcc	420
cagcacccac tactaccaag agctgcagag agacatttct gaaatgttt tgcagattta	480
taaacaaggg ggtttctgg gcctctccaa tattaaggcc aggcaggat ctgtgggtgt	540
acaatttgcact ctggcccttc gagaaggtac catcaatgtc cacgacgtgg agacacagtt	600
caatcagtat aaaacggaag cagccctctcg atataacctg acgatctcag acgtcagcgt	660
gagtgtatgtc ccatttcctt tctctgcccc gtctgggct ggggtgccag gctggggcat	720
cgcgcgtctg gtgtggctc gtgtctggc tgctgtggc attgtctatc tcattgcctt	780
ggctgtctgt cagtgtccgc gaaagaacta cgggcagctg gacatcttc cagccccggaa	840
tacctaccat cctatgagcg agtacccac ctaccacacc catggcgct atgtggcccc	900
tagcagtacc gatcgtagcc cctatgagaa ggtttctgca ggtaatggc gcagcagcct	960
ctcttacaca aacccagcag tggcagccac ttctgccaac ttgttagggc acgtcgcccg	1020
ctgagctgag tggccagccca gtgcattcc actccactca ggttcttcag ggccagagcc	1080
cctgcacccct gtttggctg gtgagctggg agttcagggtg ggctgctcac agccttccttc	1140
agaggccccca ccaatttctc ggacacttct cagtgtgtgg aagctcatgt gggccccctga	1200
gggctcatgc ctggaaagtg ttgtgggtgg ggctcccagg aggactggcc cagagagccc	1260

tgagatagcg gggatcctga actggactga ataaaacgtg gtctccact gc 1312

<210> 52  
<211> 2094  
<212> DNA  
<213> Homo sapien

<400> 52  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcgggcgggc ggggagtggg gggaccggta taaagcggta ggccctgtg cccgctccac 120  
ctctcaagca gccagcgctt gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca cccggcaccc agtctccctt cttcctgtg ctgctctca cagtgtttac 240  
agctaccaca gcccctaaac ccgcaacagt tgttacaggt tctggtcatg caagctctac 300  
cccaggtgga gaaaaggaga cttcggtac ccagagaagt tcagtgccta gctctactga 360  
gaagaatgct gtgagttatga ccagcagcgt actctccagc cacagccccg gttcaggctc 420  
ctccaccact cagggacagg atgtcactct ggccccggcc acggAACAGCAGGTTTC 480  
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctgggctc 540  
caccaccccg ccagcccacg atgtcacctc agccccggac aacaagccag ccccccggctc 600  
caccggccccc ccagcccacg gtgtcacctc ggccccggac accaggccgg ccccccggctc 660  
caccggccccc ccagcccacg gtgtcacctc ggccccggac aacaggccgg ccccccggctc 720  
caccggccccc ccagcccacg gtgtcacctc ggccccggac accaggccgg ccccccggctc 780  
tactctggtg cacaacggca cctctgccag ggctaccaca accccagcca gcaagagcac 840  
tccattctca attccccagcc accactctga tactcttacc acccttgcaccc gccatagcac 900  
caagactgat gccagtagca ctcaccatag cacggtaccc cctctcaccc cctccaatca 960  
cagcacttct ccccatgttctt ctactgggt ctctttctt ttcctgtctt ttcacatttc 1020  
aaacacctccag tttaattcct ctctggaaaga tcccagcacc gactactacc aagagctgca 1080  
gagagacatt tctgaaatgt ttttgcagat ttataaaca gggggtttc tggggctctc 1140  
caatattaag ttcaggtaca gttctgggtg tggacccagt gtggtggttg gaggggtgggt 1200  
ggtgtcatg accgttaggga gggactggtg cacttaaggt tgggggaaga gtgctgagcc 1260  
agagctggga cccgtggctg aagtgcctt ttcctgtga ccaggccagg atctgtggtg 1320  
gtacaattga ctctggcctt ccgagaaggt accatcaatg tccacgcacgt ggagacacag 1380  
ttcaatcagt ataaaacgga agcagcctct cgatataacc tgacgatctc agacgtcagc 1440  
gtgagtgtatg tgccatttcc tttctctgcc cagtctgggg ctgggggtgcc aggctggggc 1500  
atcgcgctgc tggtgctggt ctgtgttctg gttgcgtgg ccattgtcta tctcattgcc 1560

ttggctgtct	gtcagtgccg	ccgaaagaac	tacgggcagc	tggacatctt	tccagccgg	1620
gataacctacc	atcctatgag	cgagtacccc	acctaccaca	cccatggcg	ctatgtgcc	1680
cctagcagta	ccgatcgtag	cccctatgag	aaggttctg	caggtaatgg	tggcagcagc	1740
ctctcttaca	caaaccgc	agtggcagcc	acttctgcc	acttgttaggg	gcacgtcgcc	1800
cgctgagctg	agtggccagc	cagtgccatt	ccactccact	caggttcttc	agggccagag	1860
ccccctgcacc	ctgtttgggc	tggtgagctg	ggagttcagg	tgggctgctc	acagcctcct	1920
tcagaggccc	caccaatttc	tcggacactt	ctcagtgtgt	ggaagctcat	gtgggcccct	1980
gagggctcat	gcctggaaag	tgttgtggtg	ggggctccca	ggaggactgg	cccagagagc	2040
cctgagatag	cggggatcct	gaactggact	gaataaaaacg	tggtctccca	ctgc	2094

<210> 53  
<211> 2049  
<212> DNA  
<213> Homo sapien

<400> 53	taggaggtag	gggagggggc	ggggttttgt	cacctgtcac	ctgctccggc	tgtgctatgg	60
	gcggggcgggc	ggggagtggg	gggaccggta	taaagcggta	ggcgctgtg	cccgctocac	120
	ctctcaagca	gccagcgct	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctcctt	cttcctgctg	ctgctcctca	cagtgcttac	240
	agctaccaca	gcccctaaac	ccgcaacagt	tgttacaggt	tctggtcatg	caagctctac	300
	cccaggtgga	aaaaaggaga	cttcggctac	ccagagaagt	tcagtgccca	gctctactga	360
	gaagaatgct	gtgagtatga	ccagcagcgt	actctccagc	cacagccccg	gttcaggctc	420
	ctccaccact	cagggacagg	atgtcactct	ggccccggcc	acggaaccag	cttcaggttc	480
	agctgccacc	tggggacagg	atgtcacctc	ggtcccagtc	accaggccag	ccctgggctc	540
	caccaccccg	ccagcccacg	atgtcacctc	agccccggac	aacaagccag	ccccgggctc	600
	caccgcccc	ccagcccacg	gtgtcacctc	ggccccggac	accaggccgg	ccccgggctc	660
	caccgcccc	ccagcccacg	gtgtcacctc	ggccccggac	aacaggcccc	ccttgggctc	720
	cacceccct	ccagtcacata	atgtcacctc	ggcctcaggc	tctgcatcag	gctcagcttc	780
	tactctggtg	cacaacggca	cctctgccag	ggctaccaca	accccagcca	gcaagagcac	840
	tccattctca	atcccagcc	accactctga	tactcctacc	acccttgcca	gccatagcac	900
	caagactgat	gccagtagca	ctcaccatag	cacggtaacct	cctctcacct	cctccaaatca	960
	cagcacttct	ccccagttgt	ctactggggt	ctctttcttt	ttcctgtctt	ttcacatttc	1020
	aaacacctccag	tttaattcct	ctctggaaga	tcccagcacc	gactactacc	aagagctgca	1080

gagagacatt	tctgaaatgt	ttttgcagat	ttataaacaa	gggggttttc	tgcccctctc	1140
caatattaag	ttcaggccag	gatctgtggt	ggtacaattg	actctggcct	tccgagaagg	1200
taccatcaat	gtccacgacg	tggagacaca	gttcaatcg	tataaaacgg	aagcagcctc	1260
tcgatataac	ctgacgatct	cagacgtcag	cgtgagtgtat	gtgccatttc	ctttctctgc	1320
ccagtcgtgg	gctggggtgc	caggctgggg	catcgcgctg	ctggtgctgg	tctgtgttct	1380
ggttgcgtg	gccattgtct	atctcattgc	cttggctgtc	tgtcaagtgcc	gccgaaaagaa	1440
ctacgggcag	ctggacatct	ttccagcccc	ggataacctac	catoctatga	gcgagtaacc	1500
cacctaccac	accatgggc	gctatgtgcc	ccctagcagt	accgatcgta	gcccctatga	1560
gaaggtttct	gcaggtaatg	gtggcagcag	cctctttac	acaaacccag	cagtggcagc	1620
cacttctgcc	aacttgttagg	ggcacgtcgc	ccgctgagct	gagtggccag	ccagtgcct	1680
tccactccac	tcaggttctt	cagggccaga	gcccctgcac	cctgtttggg	ctggtgagct	1740
gggagttcag	gtgggctgct	cacagcctcc	ttcagaggcc	ccaccaattt	ctcggacact	1800
tctcagtgtg	tggaagctca	tgtggggcccc	tgagggctca	tgcctggaa	gtgttgtgg	1860
gggggctccc	aggaggactg	gccagagag	ccctgagata	gcggggatcc	tgaactggac	1920
tgaataaaac	gtggtctccc	actgcaaaag	acataaaaaaa	agaaaaagac	aaagacgagc	1980
aaaaagacaa	aaagaggcaa	aaacaacaaa	acacaacaaa	caaaaaaaaaag	cacacacaaa	2040
aaaaagaag						2049

<210> 54  
<211> 2194  
<212> DNA  
<213> Homo sapien

<400> 54	taggaggtag	gggagggggc	gggggtttgt	cacctgtcac	ctgctccggc	tgtgctatgg	60
	gccccccccc	ggggagtggg	gggaccggta	taaagcggt	ggcgccctgt	cccgctccac	120
	ctctcaagca	gcgcgcgc	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctccctt	cttccctgt	ctgctcctca	cagtgtttac	240
	agctaccaca	gcccctaaac	ccgcaacagt	tgttacaggt	tctggtcatg	caagctctac	300
	cccgagggt	gaaaaggaga	cttcggctac	ccagagaagt	tcaagtgc	ccatgttactga	360
	gaagaatgt	gtgagtatga	ccagcagcgt	actctccagc	cacagccccg	gttcaggctc	420
	ctccaccact	cagggacagg	atgtcactct	ggccccggcc	acggaaccag	cttcagggttc	480
	agctgccacc	tggggacagg	atgtcacctc	ggtcccagtc	accaggccag	ccctgggctc	540
	caccaccccg	ccagccccacg	atgtcacctc	agccccggac	aacaagccag	ccccgggctc	600

caccggccccc	ccagccccacg	gtgtcacctc	ggccccggac	accaggccgg	ccccgggctc	660
caccggccccc	ccagccccatg	gtgtcacctc	ggccccggac	aacaggcccg	ccttgggctc	720
caccggccccc	ccagtcacaca	atgtcacctc	ggcctcaggc	tctgcatcg	gctcagctc	780
tactctggtg	cacaacggca	cctctgccag	ggctaccaca	accccagcca	gcaagagcac	840
tccattctca	attcccagcc	accactctga	tactcttacc	acccttgcac	gccatagcac	900
caagactgat	gccagtagca	ctcaccatag	cacggtacct	cctctcacct	cctccaaatca	960
cagcacttct	ccccagttgt	ctactgggt	ctctttcttt	ttcctgtctt	ttcacatttc	1020
aaacctccag	ttaattccct	ctctggaaga	tcggcacc	gactactacc	aagagctgca	1080
gagagacatt	tctgaaatgg	tgagtatcg	cctttccctc	ccatgctcc	cctgaaggcag	1140
ccatcagaac	tgtccacacc	ctttgcatca	agcctgagtc	ctttccctct	caccccaattt	1200
ttttgcagat	ttataaaacaa	gggggttttc	tgggcctctc	aatattaag	ttcaggtaca	1260
gttctgggtg	tggacccagt	gtggtggttg	gagggtgggt	ggtggtcatg	accgttaggaa	1320
gggactggtg	cacttaaggt	tggggaaaga	gtgctgagcc	agagctggaa	cccggtggtg	1380
aagtccccat	ttccctgtga	ccagggcagg	atctgtggtg	gtacaattga	ctctggcctt	1440
ccgagaaggt	accatcaatg	tccacgacgt	ggagacacag	ttcaatcagt	ataaaaacgga	1500
agcagccctct	cgtataacc	tgacgatctc	agacgtcagc	gtgagtgtatg	tgccatttcc	1560
tttctctgcc	cagtctgggg	ctggggtgcc	aggctggggc	atcgcgctgc	tggtgctgg	1620
ctgtgttctg	gttgcgctgg	ccattgtcta	tctcattgcc	ttggctgtct	gtcagtgccg	1680
ccgaaaagaac	tacgggcagc	tggacatctt	tccagccgg	gatacctacc	atcctatgag	1740
cgagtacccc	acctaccaca	cccatggcgc	ctatgtgccc	cctagcagta	ccgatcgtag	1800
ccctatatgag	aaggtttctg	caggtaatgg	tggcagcagc	ctcttttaca	caaaccacgc	1860
agtggcagcc	acttctgccca	acttgttaggg	gcacgtcgcc	cgctgagctg	agtggccagc	1920
cagtgccatt	ccactccact	caggttcttc	agggccagag	ccctgcacc	ctgtttggc	1980
tggtgagctg	ggagttcagg	tgggctgctc	acagcctcct	tcaaggccc	caccaatttc	2040
tcggacactt	ctcagtgtgt	ggaagctcat	gtggggccct	gagggtctcat	gcctggaaag	2100
tgttgtggtg	ggggctccca	ggaggactgg	cccagagagc	cctgagatag	cggggatct	2160
gaactggact	gaataaaacg	tggtctccca	ctgc			2194

<210> 55  
<211> 1183  
<212> DNA  
<213> Homo sapien

<400> 55  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcgggcgggc ggggagtggg gggaccggta taaagcggtt ggcgcctgtg cccgctccac 120  
ctctcaagca gccagcgctt gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca ccgggcaccc agtctcctt cttcctgctg ctgctcctca cagtgcttac 240  
agtttgtaca gggtctggtc atgcaagctc taccccagggt ggagaaaagg agacttcggc 300  
tacccagaga agttcagtgc ccagctctac tgagaagaat gctatcccag caccgactac 360  
taccaagagc tgcagagaga catttctgaa atggccagga tctgtggtgg tacaattgac 420  
tctggccttc cgagaaggta ccatcaatgt ccacgacgtg gagacacagt tcaatcagta 480  
taaaacggaa gcagcctctc gatataacct gacgatctca gacgtcagcg tgagtgtatgt 540  
gccatttctt ttctctgccc agtctggggc tgggtgcca ggctggggca tcgcgctgct 600  
ggtgctggtc tgggttctgg ttgcgtggc cattgtctat ctcattgcct tggctgtctg 660  
tcagtgccgc cgaaagaact acgggcagct ggacatctt ccagccccc atacctacca 720  
tcctatgagc gagtacccca cctaccacac ccatggcgc tatgtgcccc cttagcgtac 780  
cgatcgttagc ccctatgaga aggttctgc aggtaatgggt ggcagcagcc tctcttacac 840  
aaaccaggca gtggcagcca cttctgccaa cttgttaggg cacgtcgccc gctgagctga 900  
gtggccagcc agtgcatttc cactccactc aggttcttca gggccagagc ccctgcaccc 960  
tgttggct ggtgagctgg gagttcaggt gggctgctca cagccctt cagaggcccc 1020  
accaatttct cggacacttc tcagtgtgtg gaagctcatg tggcccttg agggctcatg 1080  
cctggaaatgt gttgtggtgg gggctccctg gaggactggc ccagagagcc ctgagatagc 1140  
ggggatcctg aactggactg aataaaacgt ggtctccac tgc 1183

<210> 56  
<211> 2333  
<212> DNA  
<213> Homo sapien

<400> 56  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcgggcgggc ggggagtggg gggaccggta taaagcggtt ggcgcctgtg cccgctccac 120  
ctctcaagca gccagcgctt gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca ccgggcaccc agtctcctt cttcctgctg ctgctcctca cagtgcttac 240  
agctaccaca gcccctaaac ccgcaacagt ttttacaggt tctggtcatg caagctctac 300  
cccaggtgga gaaaaggaga cttcggtac ccagagaatg tcaatggccca gctctactga 360  
gaagaatgt gtgagttatgtt ccagcagcgt actctccac cacagccccc gttcaggcgt 420

ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag cttcagggttc	480
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctgggctc	540
caccaccccg ccagcccacg atgtcacctc agccccggac aacaagccag ccccgggctc	600
caccgccccc ccagcccacg gtgtcacctc ggccccggac accaggccgg ccccgggctc	660
caccgccccc ccagcccacg gtgtcacctc ggccccggac aacaggcccg ccttgggctc	720
caccgccccct ccagtccaca atgtcacctc ggcctcaggc tctgcatcag gctcagcttc	780
tactctggtg cacaacggca cctctgccag ggctaccaca accccagcca gcaagagcac	840
tccattctca attcccagcc accactctga tactcctacc acccttgcca gccatagcac	900
caagactgat gccagtagca ctcaccatag cacggtaacct cctctcacct cctccaaatca	960
cagcacttct ccccaagtgt ctactgggt ctctttctt ttccctgtctt ttacatattc	1020
aaacctccag tttaattctt ctctggaaga tcccagcacc gactactacc aagagctgca	1080
gagagacatt tctgaaatgt tttgcagat ttataaacaa gggggttttc tgggcctctc	1140
caatattaag ttcaaggccag gatctgttgt ggtacaattt actctggctt tccgagaagg	1200
taccatcaat gtccacgacg tggagacaca gttcaatcag tataaaacgg aagcagccctc	1260
tcgatataac ctgacgatct cagacgtcag cgtgctgtga ttggaggagg tgagaggagg	1320
taccgtgcta tggtgagtgc tactggcatc agtcttggtg ctatggctgg caagggtgtt	1380
aggagtatca gagtggtggc tgggaattga gaatggagtg ctottgctgg ctggggttgt	1440
ggtagccctg gcagaggtgc cggtgtgcac cagagttagaa gctgagccctg atgccagtag	1500
cactcaccat agcacggta ctcctctcac ctccctcaat cacagcactt ctccccagtt	1560
gtctactggg gtctttctt tttectgtc ttttcaattt caaacctcca gtttaattcc	1620
tctctggaag atcccagcac cgactactac caagagctgc agagagacat ttctgaaatg	1680
tgagtgtatgt gccatttctt ttctctgccc agtctggggc tggggtgcca ggctggggca	1740
tcgcgctgtc ggtgctggc tgggttctgg ttgcgctggc cattgtctat ctcattgcct	1800
tggctgtctg tcagtgccgc cgaaagaact acgggcagct ggacatctt ccagccgggg	1860
atacctacca tcctatgagc gagtacccca cctaccacac ccatggccgc tatgtgcccc	1920
ctagcagtac cgatcgtagc ccctatgaga aggtttctgc aggtaatggt ggcagcagcc	1980
tctcttacac aaacccagca gtggcagcca cttctgccaa cttgttagggg cacgtcgccc	2040
gctgagctga gtggccagcc agtgcattc cactccactc aggttcttca gggccagagc	2100
ccctgcaccc tggggggctt ggtgagctgg gagttcaggt gggctgtca cagcctcctt	2160
cagaggcccc accaatttctt cggacacttc tcagtggtg gaagctcatg tggcccttg	2220

agggctcatg cctgggaagt gttgtggtgg gggctcccg gaggactggc ccagagagcc 2280  
ctgagatagc ggggatcctg aactggactg aataaaaacgt ggtctccac tgc 2333

<210> 57  
<211> 1712  
<212> DNA  
<213> Homo sapien

<400> 57  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcgggcgggc ggggagtggg gggaccggta taaagcggta ggccctgtg cccgctccac 120  
ctctcaagca gccagcgcct gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca cccggcaccc agtctcctt cttcctgctg ctgctcctca cagtgcctac 240  
agctaccaca gcccctaaac ccgcaacagt tgttacaggt tctggtcatg caagctctac 300  
cccaagggtgga gaaaaggaga cttcggctac ccagagaagt tcagtgccta gctctactga 360  
gaagaatgct gtgagtatga ccagcagcgt actctccagc cacagccccg gttcaggctc 420  
ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag cttcaggctc 480  
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctgggctc 540  
caccaccccg ccagcccacg atgtcacctc agccccggac aacaagccag ccccgccgctc 600  
caccgcccccc ccagcccacg gtgtcacctc ggccccggac accagggccgg ccccgccgctc 660  
caccgcccccc ccagcccatg gtgtcacctc ggccccggac aacagggccgg ctttgggctc 720  
caccgccccct ccagtccaca atgtcacctc ggccctcaggc tctgcatcag gtcagcttc 780  
tactctggtg cacaacggca cctctgccag ggctaccaca accccagcca gcaagagcac 840  
tccattctca attcccgcc accactctga tactcctacc acccttgcac gccatagcac 900  
caagactgat gccagtagca ctcaccatag cacggtagct cctctcacct cctccaatca 960  
cagcacttct ccccaagttgt ctactgggt ctctttctt ttccctgtctt ttcacatttc 1020  
aaacccatccag ttaattcct ctctggaaaga tcccagcacc gactactacc aagagctgca 1080  
gagagacatt tctgaaatgt ggggtgccag gctggggcat cgcgctgctg gtgctggct 1140  
gtgttctgggt tgcgctggcc attgtctatc tcattgcctt ggctgtctgt cagtgcgc 1200  
gaaagaacta cggcagctg gacatcttc cagccccggta tacctaccat cctatgagcg 1260  
agtacccac ctaccacacc catggcgct atgtgcccc tagcagtagcc gatcgtagcc 1320  
cctatgagaa ggtttctgca ggtaatggtg gcagcagcct ctcttacaca aaccagcag 1380  
tggcagccac ttctgccaac ttgttagggc acgtcgcccc ctgagctgag tggccagcca 1440  
gtgcattcc actccactca ggttcttcag ggccagagcc cctgcacccct gtttgggctg 1500

58

gtgagctggg agttcagggtg ggctgctcac agccctccac agaggccccca ccaatttctc 1560  
ggacacttct cagtgtgtgg aagctcatgt gggcccccga gggctcatgc ctggaaagtg 1620  
tttgtgtggg ggctcccagg aggactggcc cagagagccc tgagatagcg gggatcctga 1680  
actggactga ataaaacgtg gtctcccact gc 1712

<210> 58  
<211> 1605  
<212> DNA  
<213> Homo sapien

<400> 58  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcggggcgggc ggggagtggg gggaccggta taaagcggtt ggcgcctgtg cccgctccac 120  
ctctcaagca gccagcgctt gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca ccgggcaccc agtctccctt cttectgctg ctgctccta cagtgtttac 240  
agttgttaca ggttctggtc atgcaagctc tacccaggt ggagaaaagg agacttcggc 300  
tacccagaga agttcagtgc ccagctctac tgagaagaat gctgtgagta tgaccagcag 360  
cgtactctcc agccacagcc ccgggttcagg ctccctccacc actcaggac agatgtcac 420  
tctggccccc gccacggAAC cagttcagg tttagctgccc acctggggac agatgtcac 480  
ctcggtccca gtcaccaggc cagccctggg ctccaccacc ccggcagccc acgtgtcac 540  
ctcggtccca gacaacaggc ccgccttggg ctccaccggc cctccagtcc acaatgtcac 600  
ctcggtccca ggctctgcat caggtcagg ttctactctg gtgcacaacg gcacctctgc 660  
cagggttacc acaacccag ccagcaagag cactccatttca tcaattccca gccaccactc 720  
tgatactcct accacccttg ccagccatag caccaagact gatgccagta gcactcacca 780  
tagcacggta cctcctctca cctcctccaa tcacagcaact tctcccaagt tgtctactgg 840  
ggtctcttcc ttttcctgt ctttcacat ttcaaaccctc cagtttaatt cctctctgga 900  
agatcccagc accgactact accaagagct gcagagagac atttctgaaa tgtgagtgtat 960  
gtgccatttc ctttctctgc ccagtctggg gctgggggc caggctgggg catcgcgctg 1020  
ctgggtctgg tctgtgttct ggttgcgtg gccattgtct atctcattgc cttggctgtc 1080  
tgtcagtgtcc gcccggaaatccatgttgc cttccatggc gctatgtgcc cccttagcgt 1140  
catccttatgttgc gcccggaaatccatgttgc cttccatggc gctatgtgcc cccttagcgt 1200  
accgatcgta gccccttatgttgc cttccatggc gctatgtgcc cccttagcgt 1260  
acaaacccag cagttgtccatgttgc cttccatggc gctatgtgcc cccttagcgt 1320  
gagttggccag ccagtgtccatgttgc cttccatggc gctatgtgcc cccttagcgt 1380

59

cctgtttggg ctggtgagct gggagttcag gtgggctgct cacagccctcc ttcagaggcc	1440
ccaccaattt ctcggacact tctcagtgtg tggaagctca tgtgggcccc tgagggctca	1500
tgcctggaa gtgttgtggt gggggctccc aggaggactg gcccagagag ccctgagata	1560
gcggggatcc tgaactggac tgaataaaac gtggtctccc actgc	1605

<210> 59  
<211> 1874  
<212> DNA  
<213> Homo sapien

<400> 59	
taggagtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg	60
gcgggcgggc ggggagtggg gggaccggta taaagcggt a ggcgcctgtg cccgctccac	120
ctctcaagca gccagcgcct gcctgaatct gttctgcccc ctccccaccc atttcaccac	180
caccatgaca cggggcaccc agtctccctt cttcctgctg ctgctccctca cagtgcctac	240
agctaccaca gcccctaaac ccgcaacagt tgttacaggt tctggtcatg caagctctac	300
cccgaggta gaaaaggaga cttcggtac ccagagaagt tcagtgccca gctctactga	360
gaagaatgct gtgagtatga ccagcagcgt actctccagc cacagccccg gttcaggctc	420
ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag cttcagggtc	480
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctgggctc	540
caccaccccg ccagcccacg atgtcacctc agccccggac aacaagccag ccccgggctc	600
caccggccccc ccagcccacg gtgtcacctc ggccccggac accaggccgg ccccgggctc	660
caccggccccc ccagcccatg gtgtcacctc ggccccggac aacaggccccg cttgggctc	720
caccggccct ccagtccaca atgtcacctc ggcctcaggc tctgcatcag gctcagctc	780
tactctggtg cacaacggca cctctgccag ggctaccaca accccagcca gcaagagcac	840
tccattctca attccctagcc accactctga tactcctacc acccttgcca gccatagcac	900
caagactgat gccagtagca ctcaccatag cacggtaacct cctctcacct cctccaatca	960
cagcacttct cccccagtgt ctactgggt ctctttctt ttcctgtctt ttcacatttc	1020
aaacctccag tttaattctt ctctggaaga tcccagcacc gactactacc aagagctgca	1080
gagagacatt tctgaaatgt ttttgcagat ttataaaca gggggtttc tgggcctctc	1140
caatattaag ttcaggccag gatctgtggt ggtacaattg actctggctc tccgagaagg	1200
taccatcaat gtccacgacg tggagacaca gttcaatcag tataaaacgg aagcagcctc	1260
tcgatataac ctgacgatct cagacgtcag cgtgagtgat gtgccatttc ctttctctgc	1320
ccagtctggg gctgggggtgc caggctgggg catcgcgctg ctggtgctgg tctgtgtct	1380

60

ggttgcgctg	gccattgtct	atctcattgc	cttggctgtc	tgtcagtgcc	gccgaaagaa	1440
ctacgggcag	ctggacatct	ttccagcccc	ggataacctac	catccttatga	gcgagtaccc	1500
cacctaccac	acccatgggc	gctatgtgcc	ccctagcagt	accgatcgta	gccccttatga	1560
gaaggtgaga	ttgggccccca	caggccaggg	gaagcagagg	gttggctgg	gcaaggattc	1620
tgaagggggt	acttggaaaa	cccaaagagc	ttggaagagg	tgagaagtgg	cgtgaagtga	1680
gcaggggagg	gcctggcaag	gatgaggggc	agaggtcaga	ggagtttgg	ggcacaggcc	1740
tgggaggaga	ctatggaaga	aagggggccct	caagaggag	tggcccaact	gccagaattc	1800
ctaaaagatc	attggccgtc	cacattcatg	ctggctggcg	ctggctgaac	tggtgccacc	1860
gtggcagttt	tgtt					1874

&lt;210&gt; 60

&lt;211&gt; 1634

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 60

taggaggtag	gggagggggc	ggggtttgt	cacctgtcac	ctgtccggc	tgtgctatgg	60
gcgggcgggc	ggggagttggg	gggaccggta	taaagcggt	ggccctgtg	cccgctccac	120
ctctcaagca	gccagcgcc	gcctgaatct	gttctgcccc	ctccccaccc	atttaccac	180
caccatgaca	cegggcaccc	agtctccctt	cttcctgctg	ctgctccctca	cagtgcctac	240
agctaccaca	gcccctaaac	ccgcaacagt	tgttacaggt	tctggtcatg	caagctctac	300
cccaggtgga	aaaaaggaga	cttcggctac	ccagagaagt	tcagtgccca	gctctactga	360
gaagaatgct	gtgagtatga	ccagcagcgt	actctccagc	cacagcccc	gttcaggctc	420
ctccaccact	cagggacagg	atgtcactct	ggccccggcc	acggaaccag	cttcagggttc	480
agctgccacc	tggggacagg	atgtcacctc	ggtcccagtc	accaggccag	ccctgggctc	540
caccaccccg	ccagcccacg	atgtcacctc	agccccggac	aacaagccag	ccccgggctc	600
caccgcccc	ccagcccacg	gtgtcacctc	ggccccggac	accaggccgg	ccccgggctc	660
caccgcccc	ccagcccacg	gtgtcacctc	ggccccggac	aacaggcccc	ccttgggctc	720
caccgcccc	ccagtcacca	atgtcacctc	ggcctcaggc	tctgcatcag	gctcagcttc	780
tactctggtg	cacaacggca	cctctgccag	ggctaccaca	accccagcca	gcaagagcac	840
tccattctca	attccccagcc	accactctga	tactcttacc	acccttgcac	gccatagcac	900
caagactgat	gccagtagca	ctcaccatag	cacggtaacct	cctctcacct	cctccaatca	960
cagcacttct	ccccagttgt	ctactggggt	ctctttctt	ttcctgtctt	ttcacatttc	1020
aaacctccag	tttaattct	ctctggaaga	tcccagcacc	gactactacc	aagagctgca	1080

61

gagagacatt	tctgaaatgt	ttttcagat	ttataaacaa	gggggttttc	ggggcctctc	1140
caatattaag	ttcaggccag	gatctgttgt	ggtacaattg	actctggcct	tccgagaagg	1200
taccatcaat	gtccacgacg	tggagacaca	gttcaatcag	tataaaacgg	aagcagcctc	1260
tcgatataac	ctgacgatct	cagacgtcag	cgtgagtgtat	gtgccatttc	cttctctgc	1320
ccagtctggg	gctggggtgc	caggctgggg	catcgcgctg	ctggtgctgg	tctgtgttct	1380
ggttgcgcgt	gccattgtct	atctcattgc	cttggctgtc	tgtcagtgc	gccgaaagaa	1440
ctacggcag	ctggacatct	ttccagcccg	ggatacctac	catcctatga	gcgagtgag	1500
ggtgtagaag	agaagaagaa	ggaggttctt	gctgtgccag	aaacccttaa	aaaaaagcga	1560
aggaatttcg	cagagctgaa	gatcaagcgc	ctgagaaaaga	agttksccaa	aagatgctc	1620
gaaaggcaag	gagg					1634

<210> 61  
<211> 943  
<212> DNA  
<213> Homo sapien

<400> 61	taggaggttag	gggagggggc	ggggtttgt	cacctgtcac	ctgtccggc	tgtgttatgg	60
	gccccggggc	ggggagttggg	gggaccggta	taaagcggta	ggcgctgtg	cccgctccac	120
	ctctcaagca	gccagcgct	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctcctt	cttcctgtg	ctgtcctca	cagtgtttac	240
	agttgttaca	ggttctggtc	atgcaagctc	taccccaggt	ggagaaaagg	agacttcggc	300
	tacccagaga	agttcagtgc	ccagctctac	tgagaagaat	gcttttaatt	cctctctgga	360
	agatcccagc	accgactact	accaagagct	gcagagagac	atttctgaaa	tggctgtctg	420
	tcaagtccgc	cgaaaagaact	acgggcagct	ggacatctt	ccagccccc	atacctacca	480
	tcctatgagc	gagtacccca	cctaccacac	ccatggcgc	tatgtgcccc	ctagcagtag	540
	cgatcgttagc	ccctatgaga	aggtttctgc	aggtaatgg	ggcagcagcc	tctcttacac	600
	aaacccagca	gtggcagcca	cttctgccaa	ctttagggg	cacgtcgccc	gctgagctga	660
	gtggccagcc	agtgccattc	cactccactc	aggttcttca	ggccagagc	ccctgcaccc	720
	tgtttggct	ggtgagctgg	gagttcaggt	gggctgctca	cagcctcctt	cagaggcccc	780
	accaatttct	cggacacttc	tcagtgtgtg	gaagctatg	tggccccctg	agggctcatg	840
	cctggaaagt	gttgtggtgg	gggctcccag	gaggactggc	ccagagagcc	ctgagatagc	900
	ggggatcctg	aactggactg	aataaaacgt	ggtctccac	tgc		943

&lt;210&gt; 62

<211> 997  
<212> DNA  
<213> Homo sapien

<400> 62  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgtccggc tggctatgg 60  
gcgggcgggc ggggagtgaa gggaccggta taaagcggtt ggccgtgtg cccgctccac 120  
ctctcaagca gccagcgct gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca cggggcaccc agtctccctt cttctgtgt ctgtccctca cagtgtttac 240  
agttgttaca gggttctggtc atgcaagctc taccccagggt ggagaaaaagg agacttcggc 300  
tacccagaga agttcagtgc ccagctctac tgagaagaat gcttgcgtcta ctgggggtctc 360  
tttcttttc ctgtcttttc acatttcaaa cctccagttt aattccctctc tggaagatcc 420  
cagcaccgac tactaccaag agctgcagag agacatttct gaaatggctg tctgtcagtg 480  
ccggcgaaag aactacgggc agctggacat cttccagcc cgggataacct accatccat 540  
gagcgagttac cccacccatgg gcgttatgtg cccctagca gtaccgatcg 600  
tagccccat gagaaggttt ctgcaggtaa tgggtggcagc agcctctttt acacaaaccc 660  
agcagtggca gccacttctg ccaacttgc gggcacgtc gcccgtgag ctgagtggcc 720  
agccagtggcc attccactcc actcagggttc ttccaggcca gagccctgc accctgttg 780  
ggctgggtgag ctgggggttc aggtggctg ctcacagccct cttccagagg ccccaccaat 840  
ttctcggaca cttctcagtg tgtggaaact catgtgggcc cctgagggtt catgcctggg 900  
aagtgttgcgt gtggggggtc ccaggaggac tggcccaagag agccctgaga tagcgggat 960  
cctgaactgg actgaataaa acgtggtctc ccactgc 997

<210> 63  
<211> 548  
<212> DNA  
<213> Homo sapien

<400> 63  
gaagccccgga atggcttacc ttgatcagca gcccgtttaa gaactacggg cagctggaca 60  
tctttccagc ccgggataacc taccatccta tgagcgagta ccccacctac cacacccatg 120  
ggcgctatgt gccccctagc agtaccgtac gtggccctta tgagaaggtt tctgcaggtt 180  
atggtggcag cagcctctt tacacaaacc cagcagtggc agccacttct gccaacttgt 240  
aggggcacgt cgccccgtga gctgagtggc cagccgtgc cattccactc cactcaggtt 300  
ttcaggggcc agagccctg caccctgttt gggctggta gctgggggtt caggtgggtt 360  
gctcacagcc tccttcagag gccccaccaa ttctcggac acttctcagtg tgggtggaa 420  
tcatgtgggc ccctgagggc tcatgcctgg gaagtgttgc ggtgggggtt cccaggagga 480

ctggcccaga gagccctgag atagcgggga tcctgaactg gactgaataa aacgtggtct 540  
cccaactgc 548

<210> 64  
<211> 1378  
<212> DNA  
<213> Homo sapien

<400> 64  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcggggcgggc ggggagtggg gggaccggta taaagcggtt ggcgcctgtg cccgctccac 120  
ctctcaagca gccagcgccct gcctgaatct gttctgc(ccc ctc(cccacc accatcacac 180  
caccatgaca ccgggcaccc agtctcc(ttt cttcctgctg ctgctcctca cagtgc(tac 240  
agctaccaca gccccta(aac ccgcaacagt tgttacaggt tctggtcatg caagctctac 300  
cccagg(tgga gaaaaggaga ctccggctac ccagagaagt tcagtgc(cca gctctactga 360  
gaagaatgct gtgagtatga ccagcagcgt actctcc(cgc cacagccccg gttcagg(c 420  
ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag cttagggtc 480  
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctggg(c 540  
caccaccccg ccagcccacg atgtcacctc agccccggac aacaagccag ccccggg(c 600  
caccggcccc ccagcccacg gtgtcacctc ggccccggac accaggccgg ccccggg(c 660  
caccggcccc ccagccccatg gtgtcacctc ggccccggac aacaggccccg ccttggg(c 720  
caccggcccc ccagtccaca atgtcacctc ggcctcaggc tctgcatcag gctcagctc 780  
tactctggtg cacaacggca cctctgccag ggctaccaca accccagcca gcaagagcac 840  
tccattctca attccccagcc accactctga tactcctacc acccttgcca gccatagcac 900  
caagactgat gccagtagca ctcaccatag cacggtaacct cctctcacct cctccaaatca 960  
cagcacttct ccccagttgt ctactgggt ctctttctt ttccctgtctt ttcacatttc 1020  
aaacctccag tttaatttct ctctggaga tcccagcacc gactactacc aagagctgca 1080  
gagagacatt tctgaaatgt tttgcagat ttataaaacaa gggggtttc tgggcctctc 1140  
caatattaag ttccaggccag gatctgtggt ggtacaattt gactctggct tccgagaagg 1200  
taccatcaat gtccacgacg tggagacaca gttcaatcag tataaaacgg aagcagcc(c 1260  
tcgatataac ctgacgatct cagacgtcag cgctgaagta ccatttcaca tcatgctgac 1320  
caatatgggc ccatggagta ccacaacg(c ggggcaatcc gatttcggca caactact 1378

<210> 65  
<211> 162

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 65

gcggccgcct actactacta ctgctcgaat tcaagcttct aacgatgtac gggctcatgc 60  
ctgggaagtg ttgtggtggg ggctcccagg aggactggcc cagagagccc tgagatagcg 120  
gggatcctga actggactga ataaaacgtg gtctccact gc 162

&lt;210&gt; 66

&lt;211&gt; 1285

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 66

taggaggtag gggagggggc ggggttttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcggggcgggc ggggagtggg gggaccggta taaagcggt aggccctgtg cccgctccac 120  
ctctcaagca gccagcgcct gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca ccgggcaccc agtctccctt cttcctgctg ctgctctca cagtgcattac 240  
agctaccaca gcccctaaac ccgcaacagt ttttacaggt tctggtcatg caagctctac 300  
cccaggtgga gaaaaggaga cttcggctac ccagagaagt tcagtgccca gctctactga 360  
gaagaatgct tttaattcct ctctggaga tcccagcacc gactactacc aagagctgca 420  
gagagacatt tctgaaatgt ttttgcagat ttataaacaa ggggttttc tgggcctctc 480  
caatattaag ttcaaggccag gatctgtggt ggtacaattt actctggct tccgagaagg 540  
taccatcaat gtccacgacg tggagacaca gttcaatcag tataaaacgg aagcagccctc 600  
tcgatataac ctgacgatct cagacgtcag cgtgagtgat gtgccatttc ctttctctgc 660  
ccagtcgtgg gctgggggtgc caggctgggg catcgctgt ctggctgtgg tctgtgttct 720  
ggttgcgtg gccattgtct atctcattgc cttggctgtc tgtcagtgcc gccgaaagaa 780  
ctacgggcag ctggacatct ttccagcccg ggataacctac catcctatga gcgagtaccc 840  
cacctaccac acccatgggc gctatgtgcc ccctagcagt accgatcgta gcccctatga 900  
gaaggttct gcaggtaatg gtggcagcag cctctcttac acaaaccag cagtggcagc 960  
cacttctgcc aacttgttagg ggcacgtcgc ccgctgagct gagtggccag ccagtgcct 1020  
tccactccac tcaggttctt cagggccaga gcccctgcac cctgtttggg ctggtgagct 1080  
gggagttcag gtgggctgct cacagcctcc ttcagaggcc ccaccaattt ctggacact 1140  
tctcagtgta tggaagctca tgtgggcccc tgagggctca tgcctggaa gtgttggtt 1200  
gggggctccc aggaggactg gcccagagag ccctgagata gcggggatcc tgaactggac 1260  
tgaataaaac gtggtctccc actgc 1285

<210> 67  
<211> 1517  
<212> DNA  
<213> Homo sapien

<400> 67  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcggggcgggc ggggagtggg gggaccggta taaagcggtt ggcgcctgtg cccgcctcac 120  
ctctcaagca gccagcgect gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
caccatgaca ccgggcaccc agtctccctt cttcctgtgt ctgctcctca cagtgcattac 240  
agctaccaca gcccctaaac ccgcaacagt tgttacaggt tctggtcatg caagctctac 300  
cccgagggtgaa gaaaaggaga cttcggtac ccagagaagt tcagtgccta gctctactga 360  
gaagaatgct tttttgcaga tttataaaca agggggttt ctgggcctct ccaatattaa 420  
gttcaggcca ggatctgtgg tggtacaatt gactctggcc ttccgagaag gtaccatcaa 480  
tgtccacgac gtggagacac agttcaatca gtataaaacg gaagcagcct ctcgatataa 540  
cctgacgatc tcagacgtca gcgtgagtga tgtgccattt ctttctctg cccagtcgtgg 600  
ggctggggtgcc ccaggctggg gcatcgcgct gctgggtgtg gtctgtgttc tggttgcgt 660  
ggccattgtc tatctcattt cttggctgt ctgtcagtgc cgccgaaaga actacgggca 720  
gctggacatc tttccagccc gggataccta ccattctatg agcgagttacc ccacctacca 780  
caccatggg cgctatgtgc cccctagcag taccgatcgt agccctatg agaaggtttc 840  
tgcaggtaat ggtggcagca gcctcttta cacaaaccca gcagtggcag ccacttctgc 900  
caactttag gggcaegtcg cccgctgagc tgagtggcca gccagtggca ttccactcca 960  
ctcaggttct tcagggccag agccctgtca ccctgtttgg gctgggtgagc tgggagttca 1020  
ggtgggctgc tcacagcctc cttcagaggc cccaccaatt tctcgacac ttctcagtgt 1080  
gtggaaagctc atgtggggccctc ctgagggctc atgcctggga agtgttgtgg tgggggctcc 1140  
caggaggact ggcccagaga gccctgagat agcggggatc ctgaactgga ctgaataaaa 1200  
cgtggtctcc cactgcaaaa aaaaaagaag actgagaagc ggtcgtaaaa ggagcgcacg 1260  
cagaggcggc tggagggcga tgacactagt gcgaaactaga gacgggagag agagtgggca 1320  
cgagccgata gataggtgtg gtggtgcggta gtcgtgtgc gggcgatggg cgggcacggg 1380  
ggatgtgtcc tacgaccgga gcggtcggtt gccgcccattgg cagtgtggag tcgcggagta 1440  
cagtcgactg gggcgactca cacgaacgta catgtacacg tgtacacgca agctacgtgt 1500  
gtgagcggca gagattg 1517

<211> 524  
<212> DNA  
<213> Homo sapien

<400> 68  
gcccgtatca gagccccccg gtagaaggca ctccatggcc tgccataacc tcctatctcc 60  
ccaggctgtc tgcgttgcc gccgaaagaa ctacggcag ctggacatct ttccagcccg 120  
ggatacctac catcctatga gcgagtaccc cacctaccac acccatgggc gctatgtgcc 180  
cccttagcgt accgatcgta gcccctatga gaaggtgaga ttggggccca caggccaggg 240  
gaagcagagg gtttggctgg gcaaggattc tgaagggggt acttggaaaa cccaaagagc 300  
ttggaagagg tgagaagtgg cgtgaagtga gcaggggagg gcctggcaag gatgagggc 360  
agaggtcaga ggagtttgg gggacaggcc tgggaggaga ctatggaaga aaggggccc 420  
caagagggag tggcccaact gccagaattc ctaaaagatc attggccgtc cacattcatg 480  
ctggctggcg ctggctgaac tggtgccacc gtggcagttt tgtt 524

<210> 69  
<211> 1949  
<212> DNA  
<213> Homo sapien

<400> 69  
agggggaaaga gagtagggag agggaaaggct taagagggga agaaatgcag gggccatgag 60  
ccaaggccta tggcagaga gaaggaggct gctgcagggg aggaggcggc caacccaggg 120  
gttactgagg ctgcccactc cccagtcctc ctggtattat ttctctggtg gccagagctt 180  
atatttctt ctgctctta ttttccttc ataaagaccc aaccctatga cttaacttc 240  
ttacagctac cacagccct aaacccgcaa cagttgttac agttctggt catgcaagct 300  
ctaccccagg tggagaaaag gagacttcgg ctacccagag aagttcagtg cccagctcta 360  
ctgagaagaa tgctgtgagt atgaccagca gcgtactctc cagccacagc cccggttcag 420  
gctcctccac cactcaggga caggatgtca ctctggcccc gccacggaa ccagcttcag 480  
gttcagctgc cacctgggga caggatgtca cctcggtccc agtcaccagg ccagccctgg 540  
gctccaccac cccgccagcc cacatgtca cctcagcccc ggacaacaag ccagccccgg 600  
gctccaccgc ccccccagcc cacgggtgtca cctcggtccc ggacaccagg ccggccccgg 660  
gctccaccgc ccccccagcc catgggtgtca cctcggtccc ggacaacagg cccgccttgg 720  
gctccaccgc ccctccagtc cacaatgtca cctcggtctc aggctctgca tcaggctcag 780  
cttctactct ggtgcacaac ggcacctctg ccagggctac cacaacccca gccagcaaga 840  
gcactccatt ctcaattccc agccaccact ctgatactcc taccaccctt gccagccata 900  
gcaccaagac ttagtgcagg agcactcacc atagcacggt acctcctctc acctcctcca 960

atcacagcac ttctccccag ttgtctactg gggctcttt cttttcctg tctttcaca	1020
tttcaaacct ccagttaat tcctctctgg aagatcccag caccgactac taccaagagc	1080
tgcagagaga catttctgaa atgttttgc agatttataa acaaggggt tttctggcc	1140
tctccaatat taagttcagg ccaggatctg tggtggtaca attgactctg gccttccgag	1200
aaggtaaccat caatgtccac gacgtggaga cacagttcaa tcagtataaa acggaagcag	1260
cctctcgata taacctgacg atctcagacg tcagcgtgag tgatgtgccat tttctttct	1320
ctgcccagtc tggggctggg gtgccaggct ggggcattcgc gctgtggtg ctggctgtg	1380
ttctgggtgc gctggccatt gtctatctca ttgccttggc tgtctgtcag tgccgcccga	1440
agaactacgg gcagctggac atcttccag cccggatac ctaccatcct atgagcaggt	1500
accccaccta ccacacccat gggcgctatg tgccccctag cagtaccat ctagccccct	1560
atgagaaggt ttctgcaggt aatggtggca gcagccttc ttacacaaac ccagcagtg	1620
cagccacttc tgccaaacttg taggggcacg tgcggcgctg agctgagtg ccagccagtg	1680
ccattccact ccactcaggt tcttcaggc cagagccct gcaccctgtt tgggctggtg	1740
agctggaggt tcaggtggc tgctcacagc ctccttcaga ggccccacca atttctcgga	1800
cacttctcag tgtgtggaaat ctcatgtggg cccctgaggg ctcatgcctg ggaagtgttg	1860
tggtgggggc tcccaggagg actggccca agagccctga gatagcgggg atcctgaact	1920
ggactgaata aaacgtggtc tcccactgc	1949

<210> 70  
 <211> 1803  
 <212> DNA  
 <213> Homo sapien

<400> 70	
ggtagcgcaa gcagaacaca gaccagcacc agcagcgcga tgccccagcc gggcaccagg	60
tctcctttct tcctgctgct gtcctcaca gtgtttacag ctaccacagc ccctaaaccc	120
gcaacagttt ttacagggttc tggcatgca agtctaccc caggtggaga aaaggagact	180
tccgttaccc agagaagttc agtgcggcagc tctactgaga agaatgctgt gagtatgacc	240
agcagcgtac tctccagcca cagccccggc tcaggctctt ccaccactca gggacaggat	300
gtcactctgg ccccgccac ggaaccagct tcagggttcag ctgccacctg gggacaggat	360
gtcacctcgg tcccagtcac caggccagcc ctgggctcca ccaccccgcc agccacagat	420
gtcacctcgg ccccgacac caggccggcc ccgggctcca ccggggccccc agccacgggt	480
gtcacctcgg ccccgacac caggccggcc ccgggctcca ccggggccccc agccatgggt	540
gtcacctcgg ccccgacac caggccggcc ttgggctcca ccggggccccc agtccacaat	600

gtcacctcg	cctcaggctc	tgcacatcaggc	tcagcttcta	ctctggtgca	caacggcacc	660
tctgccaggg	ctaccacaac	cccagccagc	aagagcactc	cattctcaat	tcccagccac	720
cactctgata	ctccttaccac	ccttgcagc	catagcacca	agactgatgc	cagtagcact	780
caccatagca	cggtacacctc	tctcacctcc	tccaatcaca	gcacttctcc	ccagttgtct	840
actggggtct	ctttctttt	cctgtctttt	cacattcaa	acctccagtt	taattcctct	900
ctggaagatc	ccagcaccga	ctactacaa	gagctgcaga	gagacatttc	tgaaatgttt	960
ttgcagattt	ataaaacaagg	gggttttctg	ggcctctcca	atattaagtt	caggccagga	1020
tctgtggtgg	tacaattgac	tctggccttc	cgagaaggta	ccatcaatgt	ccacgacgtg	1080
gagacacagt	tcaatcagta	taaaaacggaa	gcagcctctc	gatataacct	gacgatctca	1140
gacgtcagcg	tgagtgtatgt	gccatttcct	ttctctgccc	agtctgggc	tggggtgcca	1200
ggctggggca	tcgcgcgtct	ggtgctggc	tgtgttctgg	ttgcgcgtggc	cattgtctat	1260
ctcattgcct	tggctgtctg	tcagtgcgc	cgaaagaact	acgggcagct	ggacatctt	1320
ccagccccgg	atacctacca	tcctatgagc	gagtacccca	cctaccacac	ccatggcgc	1380
tatgtgcccc	ctagcagtagc	cgatcgtagc	ccctatgaga	aggtttctgc	aggtaatgg	1440
ggcagcagcc	tcttttacac	aaacccagca	gtggcagcca	cttctgccaa	ctttagggg	1500
cacgtcgccc	gctgagctga	gtggccagcc	agtgccattc	cactccactc	aggttcttca	1560
ggggccagagc	ccctgcaccc	tgtttggct	ggtgagctgg	gagttcaggt	gggctgtca	1620
cagcctcctt	cagaggcccc	accaatttct	cggacacttc	tcagtgtgt	gaagctcatg	1680
tggggcccctg	agggctcatg	cctgggaagt	gttgtggtgg	gggctccca	gaggactggc	1740
ccagagagcc	ctgagatagc	ggggatcctg	aactggactg	aataaaacgt	ggtctccac	1800
tgc						1803

<210> 71  
 <211> 1258  
 <212> DNA  
 <213> Homo sapien

<400> 71	taggaggtag	gggagggggc	gggggtttgt	cacctgtcac	ctgcgtccggc	tgtgttatgg	60
	gcggggcgggc	ggggagtggg	gggaccggta	taaagcggt	ggcgcctgtg	cccgctccac	120
	ctctcaagca	gccagcgcct	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctcctt	cttcctgtg	ctgctcctca	cagtgcattac	240
	agttgttaca	ggttctggc	atgcaagctc	taccccaggt	ggagaaaaagg	agacttcggc	300
	tacccagaga	agttcagtgc	ccagctctac	tgagaagaat	gctttaatt	cctctctgga	360

agatcccagc accgactact accaagagct gcagagagac atttctgaaa tgttttgca	420
gatttataaa caagggggtt ttctgggcct ctccaatatt aagttcaggc caggatctgt	480
ggtggtacaa ttgactctgg cttccgaga aggtaccatc aatgtccacg acgtggagac	540
acagttcaat cagtataaaa cggaagcagc ctctcgatat aacctgacga tctcagacgt	600
cagcgtgagt gatgtgccat ttcccttcctc tgcccagtct ggggctgggg tgccaggctg	660
gggcacatcgcg ctgctggtgc tggctgtgt tctggttgcg ctggcattg tctatctcat	720
tgccttggct gtctgtcagt gccgcccggaaa gaactacggg cagctggaca tctttccagc	780
ccgggataacc taccatccta tgagcggaga ccccacctac cacacccatg ggccgtatgt	840
gcccccttagc agtaccgatc gtagcccta tgagaaggtt tctgcaggta atggtggcag	900
cagccctct tacacaaaacc cagcagtggc agccacttct gccaacttgt aggggcacgt	960
cgcccgtga gctgagtggc cagccagtgc cattccactc cactcagggtt ctgcaggcc	1020
agagccctg caccctgttt gggctggta gctgggagtt caggtggct gtcacagcc	1080
tccttcagag gccccaccaa tttctggac acttctcagt gtgtggaagc tcatagtggc	1140
ccctgagggc tcatacgctgg gaagtgttgtt ggtggggct cccaggagga ctggcccaga	1200
gagccctgag atagccccggaa tcctgaactg gactgaataa aacgtggctc cccactgc	1258

<210> 72  
 <211> 2045  
 <212> DNA  
 <213> Homo sapien

<400> 72	
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgcctccggc tggctatgg	60
gcgggcgggc gggaggtggg gggaccggta taaagcggta ggcgcctgtg cccgctccac	120
ctctcaagca gccagcgctt gcctgaatct gttctcccc ctcacccaccc atttcaccac	180
caccatgaca ccgggcaccc agtctccctt ctccctgctg ctgcctctca cagtgcattac	240
agctaccaca gcccctaaac ccgcaacagt tggtacaggt tctggcatg caagctctac	300
cccaggtgga gaaaaggaga ctccggctac ccagagaagt tcagtgccca gctctactga	360
gaagaatgtt gtgagttatga ccagcagcgt actctccagc cacagccccg gttcaggctc	420
ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag ctgcagggtc	480
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctgggctc	540
caccaccccg ccagccccacg atgtcacctc agccccggac aacaagccag ccccggtc	600
caccggcccccc ccagccccacg gtgtcacctc ggccccggac accaggccgg ccccggtc	660
caccggcccccc ccagccccatg gtgtcacctc ggccccggac aacaggccccg cttgggtc	720

caccggccct	ccagtccaca	atgtcacctc	ggcctcaggc	tctgcatcg	gctcagcttc	780
tactctggtg	cacaacggca	cctctgccag	ggctaccaca	accccagcca	gcaagagcac	840
tccattctca	attcccagcc	accactctga	tactcctacc	acccttgcca	gccatagcac	900
caagactgat	gccagtagca	ctcaccatag	cacggtacct	cctctcacct	cctccaatca	960
cagcacttct	ccccagttgt	ctactgggt	ctctttcttt	ttcctgtctt	ttcacatttc	1020
aaacctccag	tttaattcct	ctctggaaga	tcccagcacc	gactactacc	aagagctgca	1080
gagagacatt	tctgaaatgg	ttagtatcgg	cctttccttc	ccatgctcc	cctgaaggcag	1140
ccatcagaac	tgtccacacc	cttgcata	agcctgagtc	cttccctct	cacccagtt	1200
tttgcagat	ttataaacaa	gggggttttc	tgggcctctc	aatattaag	ttcaggccag	1260
gatctgttgt	ggtacaattg	actctggct	tccgagaagg	taccatcaat	gtccacgacg	1320
tggagacaca	gttcaatcag	tataaaacgg	aagcagcctc	tcgatataac	ctgacgatct	1380
cagacgtcag	cgtgagtgat	gtgccatttc	ctttctctgc	ccagtctggg	gctggggtgc	1440
caggctgggg	catcgcgctg	ctggtgcctgg	tctgtgttct	ggtgcgcctg	gccattgtct	1500
atctcattgc	cttggctgtc	tgtcagtgcc	gccgaaagaa	ctacgggcag	ctggacatct	1560
ttccagcccg	ggataacctac	cattctatga	gcgagtaccc	cacctaccac	acccatggc	1620
gctatgtgcc	ccctagcagt	accatcgta	gcccctatga	gaaggttct	gcaggtaatg	1680
gtggcagcag	cctctcttac	acaaacccag	cagtggcagc	cacttctgcc	aacttgtagg	1740
ggcacgtcgc	ccgctgagct	gagtggccag	ccagtgccat	tccactccac	tcaggttctt	1800
cagggccaga	gcccctgcac	cctgtttggg	ctggtgagct	gggagttcag	gtgggctgct	1860
cacagcctcc	ttcagaggcc	ccaccaattt	ctcggacact	tctcagtgtg	tggaaagctca	1920
tgtgggcccc	tgagggctca	tgcctggaa	gtgttgttgt	gggggctccc	aggaggactg	1980
gcccagagag	ccctgagata	gcggggatcc	tgaactggac	tgaataaaac	gtggtctccc	2040
actgc						2045

<210> 73  
 <211> 1266  
 <212> DNA  
 <213> Homo sapien

<400> 73	taggaggtag	gggagggggc	ggggttttgt	cacctgtcac	ctgctccggc	tgtgctatgg	60
	gcgggcgggc	ggggagtggg	gggaccggta	taaagcgta	gggcctgtg	cccgctccac	120
	ctctcaagca	gccagcgct	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctccttt	cttcctgctg	ctgctcctca	cagtgcctac	240

agctaccaca gcccctaaac ccgcaacagt tgttacaggt tctggtcatg caagctctac 300  
 cccagggtgga gaaaaggaga ctccggctac ccagagaagt tcagtgccca gctctactga 360  
 gaagaatgct atccccagcac cgactactac caagagctgc agagagacat ttctgaaaatg 420  
 ttttgcaga tttataaaaca aggggggtttt ctgggcctct ccaatattaa gttcaggcca 480  
 ggatctgtgg tggtacaatt gactctggcc ttccgagaag gtaccatcaa tgtccacgac 540  
 gtggagacac agttcaatca gtataaaacg gaagcagcct ctcgatataa cctgacgatc 600  
 tcagacgtca gcgtgagtga tgtgccattt cctttctctg cccagtcgtgg ggctgggtg 660  
 ccaggctggg gcatcgcgct gctggtgctg gtctgtgttc tgggtgcgct ggccattgtc 720  
 tatctcatttgc cttggctgt ctgtcagtgc cgccgaaaga actacgggca gctggacatc 780  
 tttccagccc gggataccca ccattctatg agcgagtacc ccacctacca cacccatggg 840  
 cgctatgtgc cccctagcag taccgatcg agccctatg agaaggtttgc tgcaggtaat 900  
 ggtggcagca gctctctta cacaaccca gcagtggcag ccacttctgc caacttgttag 960  
 gggcacgtcg cccgctgagc tgagtggcca gccagtggca ttccactcca ctcagggtct 1020  
 tcagggccag agccctgtca ccctgtttgg gctggtgagc tggaggttca ggtggctgc 1080  
 tcacagcctc cttcagagggc cccaccaatt tctcgacac ttctcagtgt gtggaaagctc 1140  
 atgtggccc ctgagggctc atgcctggga agtgttgtgg tggggctcc caggaggact 1200  
 ggcccagaga gcccctgagat agcggggatc ctgaactggc ctgaataaaa cgtggctcc 1260  
 cactgc 1266

<210> 74  
 <211> 1189  
 <212> DNA  
 <213> Homo sapien

<400> 74  
 taggaggttag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
 gcgggcgggc ggggagtggttggg gggaccggta taaagcggtttaa ggcgcctgtg cccgctccac 120  
 ctctcaagca gccagcgctt gcctgaatct gttctggccc ctccccaccc atttcaccac 180  
 caccatgaca ccgggcaccc agtctctttt ctgcgtgtc ctgctccctca cagtgtttac 240  
 agttgttaca ggttctggtc atgcaagctc tacccctgggttgggaaagg agacttcggc 300  
 tacccagaga agttcagtgc ccagctctac tgagaagaat gctttttgc agatttataa 360  
 acaaggggtt tttctggcc tctccaatat taagttcagg ccaggatctg tgggtggtaca 420  
 attgactctg gccttcggag aaggtaccat caatgtccac gacgtggaga cacagttcaa 480  
 tcagtataaaa acggaagcag cctctcgata taacctgacg atctcagacg tcagcgttag 540

ttagtgtgcca tttcctttct ctgccaggc tggggctggg gtgcaggct ggggcattcgc 600  
 gctgctggtg ctggctgtg ttctgggtgc gctggccatt gtctatctca ttgccttggc 660  
 tgtctgtcag tgccgcccga agaactacgg gcagctggac atcttccag cccggatac 720  
 ctaccatcct atgagcgagt accccaccta ccacacccat gggcgctatg tgccccctag 780  
 cagtagccat cgtagccct atgagaaggt ttctgcaggt aatggtggca gcagcccttc 840  
 ttacacaaac ccagcagtgg cagccacttc tgccaaacttg taggggcacg tcgccccctg 900  
 agctgagtgcc agccaggta ccatccact ccactcaggt tcttcaggc cagagccct 960  
 gcaccctgtt tgggctggtg agctgggagt tcaggtggc tgctcacagc ctccctcaga 1020  
 ggccccacca atttctcgga cacttctcag tgggtggaaag ctcatgtggg cccctgaggg 1080  
 ctcatgcctg ggaagtgttg tgggtggggc tcccaggagg actggccca agagccctga 1140  
 gatagcggggg atccctgaact ggactgaata aaacgtggc tcccaactgc 1189

<210> 75  
 <211> 1216  
 <212> DNA  
 <213> Homo sapien

<400> 75  
 taggaggttag gggagggggc ggggtttgt cacctgtcac ctgcctccggc tgtgctatgg 60  
 gcggggcgggc ggggagtggtt gggaccggta taaagcggta ggccctgtg cccgctccac 120  
 ctctcaagca gccagcgcct gcctgaatct gttctgcccc ctccccaccc atttcaccac 180  
 caccatgaca cggggcaccc agtctccctt cttectgctg ctgcctctca cagtgcattac 240  
 agtaccaca gcccctaaac ccgcaacagt tggtaacgggt tctggtcatg caagctctac 300  
 cccaggtgga gaaaaggaga ctccggctac ccagagaagt tcagtgccca gctctactga 360  
 gaagaatgt tttttgcaga tttataaaca agggggtttt ctgggcctct ccaatattaa 420  
 gttcaggcca ggtatctgtgg tggtaacatt gactctggcc ttccgagaag gtaccatcaa 480  
 tgtccacgc acgtggagacac agttcaatca gtataaaacg gaaggcgcct ctcgatataa 540  
 cctgacgatc tcagacgtca gcgtgagtgta tgtgccattt cctttctctg cccagtcgtt 600  
 ggctgggggtg ccaggctggg gcatcgccgt gctgggtgtc gtctgtgttc tggttgcgt 660  
 ggccattgtc tatctcatttgc cttggctgt ctgtcagtgcc cgccgaaaga actacggca 720  
 gctggacatc tttccagccc gggataccta ccacccatgt agcgagttacc ccacccatca 780  
 caccatggg cgctatgtgc cccctagcag taccgatcgt agccctatg agaaggtttc 840  
 tgcaggtaat ggtggcagca gcctcttta cacaacccca gcagtgccag ccacttctgc 900  
 caactttag gggcacgtcg cccgctgagc tgagtggcca gccagtgccca ttccactcca 960

ctcaggttct tcagggccag agcccctgca ccctgtttgg gctggtgagc tgggagttca 1020  
ggtgggctgc tcacagcctc cttcagaggc cccaccaatt tctcggacac ttctcagtgt 1080  
gtgaaagctc atgtgggccc ctgagggctc atgcctggga agtgttgtgg tgggggctcc 1140  
caggaggact ggcccagaga gccctgagat agcggggatc ctgaactgga ctgaataaaa 1200  
cgtggtctcc cactgc 1216

<210> 76  
<211> 2090  
<212> DNA  
<213> Homo sapien

<400> 76  
taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
gcgggcgggc ggggagtggg gggaccggta taaagcggta ggcgcctgtg cccgctccac 120  
ctctcaagca gccagcgct gcctgaatct gttctgcccc ctccccaccc attcaccac 180  
caccatgaca cggggcaccc agtctcctt cttcctgctg ctgctcctca cagtgttac 240  
agctaccaca gccctaaac ccgcaacagt tgttacaggt tctggtcatg caagctctac 300  
cccaggtgga gaaaaggaga ctccggctac ccagagaagt tcagtgccca gctctactga 360  
gaagaatgct gtgagtatga ccagcagcgt actctccagc cacagccccg gttcaggctc 420  
ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag cttcagggtc 480  
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctgggctc 540  
caccaccccg ccagcccacg atgtcacctc agccccggac aacaagccag ccccggtc 600  
caccggccccc ccagcccacg gtgtcacctc ggccccggac accaggccgg ccccggtc 660  
caccggccccc ccagcccatg gtgtcacctc ggccccggac aacaggcccg cttgggctc 720  
caccggccct ccagtcacca atgtcacctc ggcctcaggg tctgcacccag gtcagcttc 780  
tactctggtg cacaacggca cctctgccag ggctaccaca accccagcca gcaagagcac 840  
tccattctca attcccgacc accactctga tactcttacc acccttgcca gccatagcac 900  
caagactgat gccagtagca ctcaccatag cacggtacct cctctcacct cctccaatca 960  
cagcacttct cccccagtgt ctactgggt ctctttctt ttccctgtt ttcacatttc 1020  
aaacctccag tttaattctt ctctggaaaga tcccagcacc gactactacc aagagctgca 1080  
gagagacatt tctgaaatgt ttttcagat ttataaaca gggggtttc tgggcctctc 1140  
caatattaag ttcaggccag gatctgtggt ggtacaattg actctggctc tccgagaagg 1200  
taccatcaat gtccacgacg tggagacaca gttcaatcag tataaaacgg aagcagocctc 1260  
tcgatataac ctgacgatct cagacgtcag cggtgaggct acttccctgg ctgcagccca 1320

gcaccatgcc	ggggccccctc	tccttccagt	gtctgggtcc	ccgcttttc	cttagtgctg	1380
gcagcgggag	gggcgcctcc	tctgggagac	tgccctgacc	actgctttc	cttttagtga	1440
gtgatgtgcc	atttccttc	tctgcccagt	ctggggctgg	ggtgcaggc	tggggcatcg	1500
cgcgtcttgt	gctggcttgt	gttctggttg	cgcgtggccat	tgtcttatctc	attgccttgg	1560
ctgtctgtca	gtgccgcga	aagaactacg	ggcagctgga	catcttcca	gcccggata	1620
cctaccatcc	tatgagcgag	taccccacct	accacaccca	tggcgctat	gtgcccccta	1680
gcagtagccg	tcgttagcccc	tatgagaagg	tttctgcagg	taatggtggc	agcagccct	1740
cttacacaaa	cccagcagt	gcagccactt	ctgccaactt	gtaggggcac	gtcgcccgct	1800
gagctgagtg	gccagccagt	gccattccac	tccactcagg	ttcttcaggg	ccagagcccc	1860
tgcaccctgt	ttgggcttgt	gagctgggag	ttcaggtggg	ctgctcacag	cctccttcag	1920
aggccccacc	aatttctcg	acacttctca	gtgtgtggaa	gctcatgtgg	gcccctgagg	1980
gctcatgcct	gggaagtgtt	gtggtggggg	ctcccaggag	gactggccca	gagagccctg	2040
agatagcggg	gatcctgaac	tggactgaat	aaaacgttgt	ctcccactgc		2090

<210> 77  
 <211> 1808  
 <212> DNA  
 <213> Homo sapien

<400> 77	taggaggtag	gggagggggc	ggggtttgt	cacctgtcac	ctgctccggc	tgtctatgg	60
	gcgggcgggc	ggggagtggg	gggaccggta	taaagcggta	ggcgcctgtg	cccgctccac	120
	ctctcaagca	gccagcgct	gcctgaatct	gttctgc	ctccccaccc	atttcaccac	180
	caccatgaca	ccggcacc	agtctc	ttcctgctg	ctgctc	cattgc	240
	agctaccaca	gccc	taaac	ccgcaacagt	tgttacagg	tctgtcatg	300
	cccagg	ggaa	aggaga	cttcggctac	ccagaga	agtgtccc	360
	gaagaatgt	gtgag	atgtatga	ccagc	aggcgt	actctcc	420
	ctccacc	cagg	gacagg	atgtc	actct	ggccggcc	480
	agctg	ccacc	atgtc	acc	ggccc	acggaa	540
	caccac	ccgg	atgtc	acc	aggcc	ccctgg	600
	cacc	ccgg	ccag	gtgtc	acc	ggcc	660
	cacc	ccgg	ccag	gtgtc	acc	ggcc	720
	cacc	ccgg	ccag	atgtc	acc	ggcc	780
	tactctgg	cacaacgg	ca	cctct	gccc	ggctacc	840

tccattctca attcccagcc accactctga tactcctacc acccttgcca gccatagcac 900  
 caagactgat gccagtagca ctcaccatag cacggtacct cctctcacct cctccaatca 960  
 cagcacttct ccccagttgt ctactgggt ctctttctt ttccctgtctt ttcacattc 1020  
 aaacctccag ttaattcct ctctggaaga tcccagcacc gactactacc aagagctgca 1080  
 gagagacatt tctgaaatgt ttttgcagat ttataaaca 9ggggttttc tgggcctctc 1140  
 caatattaag ttcagtgagt gatgtgccat ttcccttctc tgcccaagtct 9gggctgggg 1200  
 tgccaggctg gggcatcgcg ctgctggtgc tggctgtgt tctgggtgc ctggccattg 1260  
 tctatctcat tgccttggct gtctgtcagt gcccggaaa gaactacggg cagctggaca 1320  
 tctttccagc ccgggataacc taccatccta tgagcgagta ccccacctac cacacccatg 1380  
 ggcgctatgt gccccctagc agtaccgatc gttagcccta tgagaaggtt tctgcaggt 1440  
 atggggcag cagcctctct tacacaaacc cagcagtggc agccacttct gccaacttgt 1500  
 aggggcacgt cgcccgctga gctgagtgcc cagccagtc cattccactc cactcagggt 1560  
 cttcagggcc agagccctg caccctgttt gggctggta gctggagtt caggtggct 1620  
 gctcacagcc tccttcagag gccccaccaa tttctcgac acttctcagt gtgtggaaagc 1680  
 tcatgtggc ccctgagggc tcatgcctgg gaagtgttgtt ggtggggct cccaggagga 1740  
 ctggcccaga gagccctgag atagcgggaa tcctgaactg gactgaataa aacgtggct 1800  
 cccactgc 1808

<210> 78  
 <211> 1823  
 <212> DNA  
 <213> Homo sapien

<400> 78  
 taggaggtag gggagggggc ggggtttgt cacctgtcac ctgctccggc tgtgctatgg 60  
 gcgggcgggc ggggagtggtt gggaccggta taaagcggtt ggccctgtg cccgctccac 120  
 ctctcaagca gccagcgctt gcctgaatct gttctgcctt ctcacccaccc atttcaccac 180  
 caccatgaca cccggcaccc agtctccctt cttccctgtc ctgctcctca cagtgtttac 240  
 agtaccaca gcccctaaac ccgcaacagt ttttacaggt tctggctatg caagctctac 300  
 cccaggtgga gaaaaggaga cttcggctac ccagagaagt tcagtgccca gctctactga 360  
 gaagaatgt gtgagttatga ccagcagcgt actctccaccc cacagccccg gttcaggctc 420  
 ctccaccact cagggacagg atgtcactct ggccccggcc acggaaccag cttcagggttc 480  
 agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctggctc 540  
 caccaccccg ccagccacg atgtcacctc agccccggac aacaagccag ccccggttc 600

caccggcccc	ccagccccacg	gtgtcacctc	ggccccggac	accaggccgg	ccccgggctc	660
caccggcccc	ccagccccatg	gtgtcacctc	ggccccggac	aacaggcccg	ccttgggctc	720
caccggcccc	ccagtccaca	atgtcacctc	ggcctcaggc	tctgcacatcg	gttcagcttc	780
tactctggtg	cacaacggca	cctctgccag	ggctaccaca	accccagcca	gcaagagcac	840
tccattctca	attcccagcc	accactctga	tactcctacc	acccttgcca	gccatagcac	900
caagactgat	gccagtagca	ctcaccatag	cacggtaacct	cctctcacct	cctccaatca	960
cagcacttct	ccccagttgt	ctactgggt	ctctttcttt	ttcctgtctt	ttcacatttc	1020
aaacctccag	tttaattcct	ctctggaaaga	tcccagcacc	gactactacc	aagagctgca	1080
gagagacatt	tctgaaatgt	ttttgcagat	ttataaaacaa	gggggttttc	tgggcctctc	1140
caatattaag	ttcaggccag	gatctgttgt	ggtacaattt	actctggct	tccgagaagg	1200
taccatcaat	gtccacgacg	tggagacaca	gttcaatcg	tataaaacgg	aagcagccctc	1260
tcgatataac	ctgacgatct	cagacgtcag	cggctgtctg	tcagtgccgc	cgaaaagaact	1320
acgggcagct	ggacatctt	ccagccccgg	atacctacca	tcctatgagc	gagtacccca	1380
cctaccacac	ccatgggcgc	tatgtgcccc	ctagcagttac	cgatcgtagc	ccctatgaga	1440
aggtttctgc	aggtaatgg	ggcagcagcc	tctcttacac	aaacccagca	gtggcagcca	1500
cttctgccaa	ctttaggggg	cacgtcgccc	gctgagctga	gtggccagcc	agtgccattc	1560
cactccactc	aggttcttca	ggccagagc	ccctgcaccc	tgtttggct	ggtgagctgg	1620
gagttcagg	gggctgtca	cagcctcctt	cagaggcccc	accaatttct	cgacacttc	1680
tcagtgtgt	gaagctcatg	tggcccccctg	agggctcatg	cctggaaagt	gttgcgtgg	1740
gggctcccag	gaggactggc	ccagagagcc	ctgagatagc	ggggatcctg	aactggactg	1800 ..
aataaaacgt	ggtctccac	tgc				1823

<210> 79  
 <211> 1630  
 <212> DNA  
 <213> Homo sapien

<400> 79	taggaggtag	gggagggggc	ggggtttgt	cacctgtcac	ctgtccggc	tgtgctatgg	60
	gccccccggc	ggggagtggg	gggaccggta	taaagcggt	ggccctgtg	cccgctccac	120
	ctctcaagca	gccagcgct	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctccctt	cttcctgctg	ctgtcctca	cagtgcattac	240
	agctaccaca	gcccctaaac	ccgcaacagt	tgttacaggt	tctggtcatg	caagctctac	300
	cccaggtgga	gaaaaggaga	cttcggctac	ccagagaagt	tcagtgccca	gctctactga	360

gaagaatgct gtgagtatga ccagcagcgt actctccagc cacagccccg gttcaggctc	420
ctccaccact cagggacagg atgtcacctc ggccccggcc acggaaccag cttaggttc	480
agctgccacc tggggacagg atgtcacctc ggtcccagtc accaggccag ccctgggctc	540
caccaccccg ccagcccacg atgtcacctc agccccggac aacaagccag ccccccggctc	600
caccgcccccc ccagcccacg gtgtcacctc ggccccggac accaggccgg ccccccggctc	660
caccgcccccc ccagccccatg gtgtcacctc ggccccggac aacaggccccg ccttgggctc	720
caccgccccct ccagtccaca atgtcacctc ggcctcaggc tctgcacatc gtcacatc	780
tactctggtg cacaacggca cctctgccag ggctaccaca accccagcca gcaagagcac	840
tccattctca attcccagcc accactctga tactcctacc acccttgcca gccatagcac	900
caagactgat gccagtagca ctcaccatag cacggtaacct cctctcacct cctccaaatca	960
cagcacttct ccccagttgt ctactgggt ctctttcttt ttccctgtctt ttccacatttc	1020
aaacccctccag tttaattctt ctctggaaga .tcccagcacc gactactacc aagagctgca	1080
gagagacatt tctgaaaatgg ctgtctgtca gtggccggaa aagaactacg ggcagctgga	1140
catcttcca gcccgggata cctaccatcc tatgagcggag taccccacct accacaccca	1200
tggcgctat gtgcccccta gcagtaccga tcgttagcccc tatgagaagg tttctgcagg	1260
taatggtggc agcagccctct cttacacaaaa cccagcagtgc gcagccactt ctgccaactt	1320
gttagggcacc gtgcggccgtc gagctgagtg gccagccagt gccattccac tccactcagg	1380
ttcttcaggc ccagagcccc tgccaccatgt ttgggcttgt gagctgggag ttccaggtggg	1440
ctgctcacag cctcttcag aggccccacc aatttctcgg acacttctca gtgtgtggaa	1500
gctcatgtgg gcccctgagg gctcatgcct gggaaagtgtt gtgggtgggg ctcccaggag	1560
gactggccca gagagccctg agatagcggg gatccctgaac tggactgaat aaaacgtgg	1620
ctcccaactgc	1630

<210> 80  
 <211> 640  
 <212> DNA  
 <213> Homo sapien

<400> 80	
agtcgtgacg tggcacaacc ctggcgctgg ggtgccaggc tggggcatcg cgctgcttgt	60
gctggcttgt gttctggttg cgctggccat tgtctatctc attgccttgg ctgtctgtca	120
gtggccggaa aagaactacg ggcagctgga catcttcca gcccgggata cctaccatcc	180
tatgagcggag taccccacct accacaccca tggcgctat gtgcccccta gcagtaccga	240
tcgtagcccc tatgagaagg tttctgcagg taatggtggc agcagccctct cttacacaaaa	300

cccagcagtgcagccacttctgccaacttgtagggcacgtcgccgctgagctgagtg 360  
 gcccaggactgccattccacccactcaggttttcagggccagagcccctgtcaccctgt 420  
 ttgggctgggtgagctggagttcaggtggctgctcacagcctccttcaggaggccccacc 480  
 aatttctcggaacttctcagtgtgtggaa gctcatgtggcccccgtgagg gctcatgcct 540  
 gggaaagtgttgtgggtttcccaaggagactggccca gagagccctg agatagcggg 600  
 gatcctgaactggactgaataaaacgtggctcccaactgc 640

<210> 81  
 <211> 874  
 <212> DNA  
 <213> Homo sapien

<400> 81  
 taggaggttagggagggggcgggggtttgtcacctgtcacctgctccggctgtgctatgg 60  
 gcggggcggggcggggagtggggaccggtaaaagcggttaaaagcggttaaaagcggtggcc 120  
 ctctcaagca gccagcgcctgcgtaatctgttctgtcccccacccatttcaccac 180  
 caccatgaca ccgggcacccagtctcccttcttcctgtctgctccctca cagtgttac 240  
 agttgttaca gttctggtcatgcaagctc taccggcagggtggaaaaaggagacttcggc 300  
 taccggagaagttcagtgccagctctac tgagaagaatgctgctgtctgtcagtgcc 360  
 ccgaaagaac tacgggcagctggacatcttccagccgggataacctaccatcctatgag 420  
 cgagtacccacctaccacacccatggcgctatgtgcccctagcagtaccgatcgtag 480  
 cccctatgaaaggttctgcggtaatggtggcagcagctcttacaaacccagc 540  
 agtggcagccacttctgccaactttaggggcacgtcgcccgctgagctgagtggccagc 600  
 cagtgccattccactccactcagggttctcaggccagagccctgcaccctgtttgggc 660  
 tggtagctggagttcaggtaggtggctgctc acagcctcttcagggcccccaccaatttc 720  
 tcggacacttctcgtgtgttgcagctcatgtggccctgagggtctcatgcctggaaag 780  
 tggtagctgggtggggctccca ggaggactggccagagccctgagatagcgggatcct 840  
 gaactggactgaataaaacgtggctcccactgc 874

<210> 82  
 <211> 1084  
 <212> DNA  
 <213> Homo sapien

<400> 82  
 ttttgcttttttgcacccaggaggaaaatgggtggagcacatgcccaggggcccttc 60  
 ccgaggagtc ccagggtga gctctgtgc ccctaattcatctcctaggaa tggaggtag 120

79

accgagaaaag	gctggcatag	ggggagggtt	cccaggtaga	agaagaagtg	tcagcagacc	180
aggtgagcgt	gggtgccagt	ggggttcttg	ggagcttcaa	ggaagcaagg	aacgctccct	240
ccttcctctc	ctggcttttc	tctatggac	ctagtaaaata	attactgcag	ccacctgagg	300
ctggaaaaacc	actccaggtg	ggggaggaga	gagtttagtt	ttcttgctcc	tatttcctc	360
ctcctggaga	cctccctctc	tcggcttac	aaagacacag	atacaccccg	ccccccaaac	420
acacacacac	acacacacac	acaccctcctt	aggctggaac	agcagagaat	ggagggacaa	480
ggggctgtat	tagagccaag	aagagggagt	gaaggagagc	agagggagga	gggcagccct	540
gtttacagtc	acctggctgg	tggggtggca	ggtgctctct	ctgaattaac	cctttgagag	600
ctggccagga	ctctggactg	attacccag	cctggggtg	catccagggg	ctctaggagg	660
tacctttgc	tcctcacccct	ggatctcttt	tccttccacc	caggttctg	caggtaatgg	720
tggcagcgc	ctcttttaca	caaaccgc	agtggcagcc	acttctgc	acttgttaggg	780
gcacgtcgcc	cgctgagctg	agtggccagc	cagtgcatt	ccactccact	caggttcttc	840
agggccagag	cccctgcacc	ctgtttgggc	tggtgagctg	ggagttcagg	tgggctgctc	900
acagcctctt	tcagaggccc	caccaatttc	tcggacactt	ctcagtgtgt	ggaagctcat	960
gtggggccct	gagggctcat	gcctgggaag	tgttgtggtg	ggggctccca	ggaggactgg	1020
cccagagagc	cctgagatag	cggggatcct	gaactggact	gaataaaacg	tggtctccca	1080
ctgc						1084

<210> 83  
<211> 1194  
<212> DNA  
<213> Homo sapien

<400> 83	taggaggtag	gggagggggc	ggggttttgt	cacctgtcac	ctgctccggc	tgtgctatgg	60
	gcgggcgggc	ggggagtggg	gggaccggta	taaagcgta	ggccctgtg	cccgctccac	120
	ctctcaagca	gccagcgact	gcctgaatct	gttctgcccc	ctccccaccc	atttcaccac	180
	caccatgaca	ccgggcaccc	agtctccctt	cttcctgctg	ctgctcctca	cagtgcattac	240
	agctaccaca	gcccctaaac	ccgcaacagt	tgttacaggt	tctggtcatg	caagctctac	300
	cccaggtgga	gaaaaggaga	cttcggctac	ccagagaagt	tcagtgc	ccca gctactga	360
	gaagaatgct	gtgagtgatga	ccagcagcgt	actctccagc	cacagccccg	gttcaggctc	420
	ctccaccact	cagggacagg	atgtcactct	ggccccggcc	acgaaaccag	cttcagggttc	480
	agctgccacc	tggggacagg	atgtcaccc	ggtcccagtc	accaggccag	ccctgggctc	540
	caccaccccg	ccagccacg	atgtcaccc	agccccggac	aacaagccag	ccccgggctc	600

cacccggcccc	ccagccccacg	gtgtcacctc	ggcccccggac	accaggccgg	ccccggggtc	660
cacccggcccc	ccagccccatg	gtgtcacctc	ggcccccggac	aacaggccccg	ccttggggtc	720
cacccggcccc	ccagtcacaca	atgtcacctc	ggcctcaggc	tctgcacatcg	gtcgacttc	780
tactctggtg	cacaacggca	cctctgccag	ggctaccaca	accccagcca	gcaagagcac	840
tccattctca	atccccagcc	accactctga	tactccttacc	acccttgcca	gccatagcac	900
caagactgat	gccagtagca	ctcaccatag	cacggtaacct	ccttcacact	cctccaaatca	960
cageacttct	ccccagttgt	ctactgggt	ctctttcttt	ttccctgttctt	ttcacatttc	1020
aaacctccag	tttaattcct	ctctggaaga	tcccagcacc	gactactacc	aagagctgca	1080
gagagacatt	tctgaaatgt	ttttgcagat	ttataaaacaa	gggggttttc	tgggcctctc	1140
caatattaag	ttcagccagg	agctgtggtg	gcagaataag	cgatcctcta	atca	1194

<210> 84  
<211> 2623  
<212> DNA  
<213> Homo sapien

<400> 84	ctggaatctg	gacacacagg	gctccccccc	gcctctgact	tctctgtccg	aagtccggac	60
	accctcctac	cacctgtaga	gaagcgggag	tggatctgaa	ataaaaatcca	ggaatctggg	120
	ggttcctaga	cggagccaga	cttcggAACG	ggtgtcctgc	tactcctgct	ggggctccctc	180
	caggacaagg	gcacacaact	ggttccgtta	agccctcttc	tcgctcagac	gccatggagc	240
	tggatctgtc	tccacactcat	cttagcagct	ctccggaaaga	cctttgccc	gcccctggga	300
	ccctccctgg	gactccccgg	ccccctgata	cccccctgtcc	tgaggaggta	aagaggtccc	360
	agcctctct	catccccaaacc	accggcagga	aacttcgaga	ggaggagagg	cgtgccacct	420
	ccctccccctc	tatccccaaac	ccctccctg	agctctgcag	tcctccctca	cagagcccaa	480
	ttctcgggggg	cccccctccagt	gcaagggggc	tgctcccccg	cgatgccagc	cgccccccatg	540
	tagtaaaggt	gtacagttag	gatggggcct	gcaggtctgt	ggaggtggca	gcaggtgcca	600
	cagctcgcca	cgtgtgtgaa	atgtgtgtgc	agcgagctca	cgccttgcagc	gacgagacact	660
	gggggctgg	ggagtgccac	ccccacccatg	cactggagcg	gggtttggag	gaccacgagt	720
	ccgtgggtgga	agtgcaggct	gcctggcccg	tggcgaggaga	tagccgttc	gtctccgga	780
	aaaacttcgc	caagtacgaa	ctgttcaaga	gctccccaca	ctccctgttc	ccagaaaaaa	840
	tggtctccag	ctgtctcgat	gcacacactg	gtatatccca	tgaagacctc	atccagaact	900
	tcctgaatgc	tggcagctt	cctgagatcc	agggcttct	gcagctgcgg	ggttcaggac	960
	ggaagctttg	gaaacgcttt	ttctgcttct	tgccggatc	tggcctctat	tactccacca	1020

agggcacctc	taaggatccg	aggcacctgc	agtacgtggc	agatgtgaac	gagtccaaacg	1080
tgtacgtggt	gacgcagggc	cgcaagctct	acgggatgcc	cactgacttc	ggtttctgtg	1140
tcaagccaa	caagcttcga	aatggccaca	aggggcttgc	gatcttctgc	agtgaagatg	1200
agcagagccg	cacctgctgg	ctggctgcct	tccgccttt	caagtacggg	gtgcagctgt	1260
acaagaatta	ccagcaggca	cagtctegcc	atctgcattcc	atcttgtttg	ggctccccac	1320
ccttgagaag	tgcctcagat	aataccctgg	tggccatgga	cttctctggc	catgctggc	1380
gtgtcattga	gaaccccccgg	gaggctctga	gtgtggccct	ggaggaggcc	caggcctgga	1440
ggaagaagac	aaaccaccgc	ctcagcctgc	ccatgccagc	ctccggcacg	agcctcagtg	1500
cagccatcca	ccgcacccaa	ctctggttcc	acgggcgcat	ttcccgtag	gagagccagc	1560
ggcttattgg	acagcagggc	ttggtagacg	gcctgttcc	ggtccgggag	agtcagcgga	1620
accccccagg	ctttgtcctc	tctttgtgcc	acctgcagaa	agtgaagcat	tatctcatcc	1680
tgccgagcga	ggaggagggc	cgcctgtact	ttagcatgga	tgtggccag	acccgcttca	1740
ctgacctgct	gcagctcg	gagttccacc	agctgaaccg	cggcatcctg	ccgtgcttgc	1800
tgccgcattg	ctgcacgcgg	gtggccctct	gaccaggccg	tggactggct	catgcctcag	1860
cccgccattca	ggctgcccgc	cgcccttcca	ccatccagt	ggactctggg	gcgcggccac	1920
aggggacggg	atgaggagcg	ggagggttcc	gccactccag	ttttctcttc	tgcttcttg	1980
cctccctcag	atagaaaaca	gccccactc	cagtccactc	ctgacccctc	tcctcaaggg	2040
aaggccttgg	gtggccccc	ctccttctcc	tagctctgga	ggtgctgctc	tagggcaggg	2100
aattatggga	gaagtggggg	cagcccagc	ggtttcacgc	cccacactt	gtacagacgc	2160
agaggccagt	tgatctgctc	tgtttatac	tagtacaat	aaagattatt	ttttgataaa	2220
aaactcagaa	ctatctcg	gcgagttga	taaaaaagtgt	aaaaaaaaactg	gggggaactt	2280
catagggggt	caaacatctc	gctgccggcg	gataggactt	ggctaaactt	cttccgagcg	2340
ggccccgtaa	gggtggatg	ctgataaaaa	tgggggggggg	ccccctctc	agggggccct	2400
ccagaacctt	ttgggggtgg	ggtacccttg	ggtggtaac	tagtgaactc	tttctctaaa	2460
agggtgccgc	cccctgtgta	ttgtcgacaa	ttttcttggg	gggcggggccc	gttttctttt	2520
caccacgctt	ttgtttccc	gggtggggaa	cccacccctg	gtgtgtgtgc	cccccccgtt	2580
tatTTgggc	gcccttttg	tggggggaaa	ttcccccgct	ttt		2623

<210> 85  
<211> 1036  
<212> DNA  
<213> Homo sapien  
  
<400> 85

82

ctgagaggca	gcgaactcat	cttgcctagt	acaggagctt	gtgccgtggg	cccacagccc	60
acagccccaca	gcctatggtaa	ggcagatgtc	acaggtgggg	ggaggtgggc	tctgtgccag	120
ccaaatttcg	tctccctccc	ccagccaagg	tctcccaggg	gtgcagggag	agcggagctg	180
ctcagagctt	ggccagggttc	taagtgtgt	cctgaaagca	ggtcacccct	gagatcctca	240
gggtggggca	cagaggggca	cccttagcagg	taaaggggagg	ccacgggatg	gcgggtggca	300
gctggcccttc	tagtaacgag	ccctcagtgc	cttctgtgcc	tggggtccct	gccgacggga	360
tgttagaggac	agacaggagg	gagcactgtc	cctgggtaca	ggagctcgcc	ctgcagccag	420
tgccttgtgt	gtgggtggcc	tggggctggc	gcccgcagtct	ctgaacctgt	gtgacgcctg	480
cagggctggg	acctgacgggt	gaagatgtc	gcccccaacg	aattccaggt	gtccctgagc	540
agctccatgt	cggtgtcaga	gctgaaggcg	cagatcaccc	agaagatcgg	cgtgcacgcc	600
ttccagcagc	gtctggctgt	ccacccgagc	ggtgtggcgc	tgcaggacag	ggtccccctt	660
gccagccagg	gcctggggcc	cggcagcacg	gtcctgctgg	tggtgacaa	atgcgacgaa	720
cctctgagca	tcctggtgag	gaataacaag	ggccgcagca	gcacctacga	ggtgcggctg	780
acgcagaccc	tggcccaccc	gaagcagcaa	gtgagcgggc	tggaggggtgt	gcaggacgac	840
ctgttctggc	tgaccttcga	ggggaaagccc	ctggaggacc	agctcccgt	gggggagttac	900
ggcctaaggc	ccctgagcac	cgtgttcatg	aatctgcgcc	tgcggggagg	cggcacagag	960
cctggcgggc	ggagctaagg	gccccaccag	catccgagca	ggatcaaggg	ccggaaataaa	1020
aggctgttgt	aaagag					1036

<210> 86  
<211> 753  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (168)..(208)  
<223> n=a, c, g, or t

<400> 86	gctgcctcta	tagtgctgg	tatataagta	ttatcgacat	catttaagta	atgattttaga	60
	agttacataa	aaaaaaaaatt	tccccaaagtt	attttctggc	gaagagcttc	cctggtatga	120
	cctgaaaactc	aaacttggaa	aagagataaa	ttaattgga	taaaaatnnn	nnnnnnnnnn	180
	nnnnnnnnnn	nnnnnnnnnn	nnnnnnnnntc	tcctgaatct	tttatctatg	ccttaagcct	240
	tttctgttcc	cttcaggacc	taggctttg	aaacccaaaa	gccaggaaaa	catgcctttg	300
	ttatctgttt	tctgcaatca	cgtctttcc	atggggcact	gagcagagaa	tggtgtggcc	360

aagttagtgc	tgagaagcag	tgaggaggtg	ttagcttaggt	gtctgttccc	attttagaaa	420
atactgttcc	tacatcagaa	ataccacatt	aagacgtata	gagccaggta	actgggatgc	480
ttgaacccaa	atagctggaa	ttctggacag	agttagcaga	gtacagaagg	ctctgaagt	540
ggagacggag	ctggggtgca	tccctccca	tgaggagggg	tcatgagggg	cgtctggaa	600
gaggacatt	tgaacttagga	tttagctgagt	tgccatgatg	ctaagataat	gggagagtgt	660
tctttgtggt	caccagtgtc	cacatggcat	cccttcctg	agatttcat	cactccctgt	720
ggtcttcagt	cagtaaagct	cttagaacac	ttt			753

<210> 87  
<211> 878  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (282)..(322)  
<223> n=a, c, g, or t

<400> 87						
cgaggccga	ggttgcggtg	agctaagatc	gtacccttgc	actccagcct	gggtgacgga	60
gtaagactcc	atctccaaaa	agaaaagaag	aattgatatt	gatattggaa	gggagctgcc	120
tctataggtg	ctggtatata	agtattatcg	acatcattta	agtaatgatt	tagaagttac	180
ataaaaaaaaa	aatttccccca	agttattttc	tggcgaagag	cttccctgg	atgacactgaa	240
actcaaactt	ggaaaagaga	taaatttaat	tggataaaaa	tnnnnnnnnnn	nnnnnnnnnnn	300
nnnnnnnnnnn	nnnnnnnnnnn	nntctcctga	atctttatc	tatgccttaa	gcctttctg	360
ttcccttcag	gacctaggct	tttggaaaccc	aaaagccagg	aaaacatgcc	tttggatct	420
gttttctgca	atcacgtctc	ttccatgggg	cactgagcag	agaatgggt	ggccaagtga	480
gttagtgagaa	gcagtgagga	ggtgtgagct	agggtctgt	tcccatttt	gaaaatactg	540
ttccctacatc	agaaatacca	cattaagacg	tatagagcca	ggtcactggg	atgcttgaac	600
ccaaatagct	gggattctgg	acagagtcag	cagagtacag	aaggctctga	agtgggagac	660
ggagctgggg	tgcattccctc	ccagtgaggaa	ggggcatga	ggggcgtctg	ggaagagggaa	720
catttgaact	aggattagct	gagttgccat	gatgctaaga	taatggaga	gtgttcttg	780
tggtcaccag	tgtccacatg	gcatcccttc	cctgagattt	tcatcactcc	ctgtggtctt	840
cagtcagtaa	agctctttaga	acacttaaaa	aaaaaaaaa			878

<210> 88  
<211> 1020  
<212> DNA

<213> Homo sapien

<400> 88

caaatgcaca gtccccctcc cactccgtta cctaactgta cgtttttca tgtttataaa 60  
ctatacagaa aactgtattt gctgaactaa ggattgtatt ggtgatttct agcaaaaaca 120  
aagtgataga atttttgtct agaatccaa actggcaacg atagtctcca agggacctgg 180  
ccttgccaaag ggcctggggc aaggtgtcg cggtacgggtg aggaaggggg aggccagcaag 240  
agtcactttg ggggaccaat attcttagat atttagagca tcaccttgtt tttatatgca 300  
acacaaggct gtctgccacc ctggagcgcc ctgtcacccc tgctgtcgta gctgttgct 360  
tcagggtgag aagtgagaag cagcttattt tatatgaggg agccaggccc cgagggtgag 420  
cgagatggag aaggggaaagg aaggggcttt gggatctgga aaccagcagg ccaggcagca 480  
tccacagtgt tagtccaaag ggtcgaccg tgctgtcagc ctgcgtttg gtcagtgacg 540  
gcctggacgg gccaaggaga ctccggctt gagcccaggc ctccgcacg gtcagctgc 600  
tgaattttc cttgaggctg tttggtgtgt gaccaggcaaa gggccctgtg tgggacagca 660  
ggagggaggc gtgcggggc cttagcagaa gggaaacaat gagggcattt catgaaccat 720  
ctcaggcact tctgcatcac ggaagacctg gccctccag ccgtcctggg gatgctcagg 780  
gtgcaggcag aggctcgaaa ggccggactc aggggtcaga agcaggact gggcaggcg 840  
agcccgaca gggaaagaggg gtcggatca aagccggccg tgctgtggc cggggccca 900  
ggtgggtaca agctccttg tgcttgacaa acacctaatt ccccccacca agaggatgtg 960  
tgtgaggagc cagaaacgct gaatccaatt aagagagaaa aataataata acgaatgacg 1020

<210> 89

<211> 1854

<212> DNA

<213> Homo sapien

<400> 89

ctggggctgg cggtcactct ccgcgtgagga cccagggcgt cacacccagc actgccacat 60  
gtccaccaag gaacagaatt tattttcttc ttttttaac aagtggaaaga tctgctgggt 120  
ttcaggaaaa ggctggtaga ggcttcggct gctgtctgga cgtctggacc ctgcatttg 180  
gattataaac ccaaagtgtt cagccctagg cgggaggggg tggcgcttct cagccggctg 240  
tcccagccag ccccgccagag cgcccaacggc cagtgtccac tctggcaagg tggaaaagg 300  
cactccaagt gcatcctcca ctggcaacag tggacaatt gccccgacg gggccacccgg 360  
ggctctgtgg aatcccgatc gttccgagag gtctggaggg cccctgtggtt cctggagaaa 420  
gcaggacgca gagaagaaca aatgaggctc acccacgagg ctgggtggcc agcagtctgg 480  
gcacacacga gcaggtggca tcttggctct tgccctgagggc cagtcaccct gcccgttaatt 540

ctaccctact ccacccatcg cccctccccgc gggggtagcg cctctcattc ctgatgtctc	600
aggcaaccct ggcagaccca ggtccaaactg ctggggtcca agaaccaatt accaaaggaa	660
agatcatcag aggctgaaat ctagaacttc atcccggca atgaggttct cacagaagg	720
gcagtttat aactaactac gtccacttat atatattcac actctacata tatatatata	780
tatatatata tatatatatacacaatgca cagtcggctt cccactccgt	840
tacctaactg tacgtcttt catgttata aactatacag aaaactgtat ttgctgaact	900
aaggattgta ttggtgattt ctagaaaaaa caaagtgata gaattttgt ctagaatccc	960
aaactggcaa cgatagtctc caagggacct ggccctgcca agggctggg gcaagggtgc	1020
ggcgggacgg tgaggaaggg ggaggcagca agagtcactt tggggacca atattcttag	1080
atatttagag catcaccttg ttttatatg caacacaagc ctgtctgcca ccctggagcg	1140
ccctgtcacc cctgtgtcg tagctgtgg ctccagggtg agaagtgaga agcagctt	1200
tgtatatgag ggagccaggc cccgagggtg agcgagatgg agaagggaa ggaagggct	1260
ttggatctg gaaaccagca ggccaggcag catccacagt gtttgtccaa agggtcggac	1320
cgtgtcgta gcctagcggtt tggtcagtga cggccctggac gggccaagga gactccggc	1380
tttagccag gcctcccgca cggctcagct gctgaatttt tccttgaggc tttttgtgt	1440
gtgacccagc aagggccctg tgtggacag caggagggag gcgtcgccgg gccttagcag	1500
aagggaaca atgagggat ttcatgaacc atctcaggca ctctgcata acggaagacc	1560
tggccctccc agccgtcctg gggatgctca ggggtgcaggc agaggctcg gaggccggac	1620
tcaggggtca gaagcaggga ctggggcagg cgagccggga cagggaaagag gggctccgat	1680
caaagccggc cgtgtcgctg gcggggggcc caggtggta caagctcctt tgtgtttgc	1740
acaaaacctga atccccacc agagaggatg tgtgtgagga gccagaaaacg ctgaatccaa	1800
ttaagagaga aaaataataa taacaataaa tgatcttggca caagaaaaaaa aaaa	1854

<210> 90  
 <211> 1759  
 <212> DNA  
 <213> Homo sapien

<400> 90	
atgtaaaaag aaaatagttt tctgtgtttt gtgttgtgtt ctctcctaaa gtttaccaga	60
cgtgaagcca aaaacatcaa ctggactga caacacaaga aagattcttt aactgagg	120
gttaaatggc cctgaaaaga gcctttggag acaaagcagc cggcgacccg cggaggagg	180
gagggaggga gcgagcggc gccaggtccc ggcaggact cacttggagc tggcgtactt	240
ggtagccgccc ttggtgccct cggacacggc gtgcttggcc agctcgccgg gcagcagc	300

gcgcacggcc	gtctggatct	ccgggacgtg	atggtggagc	gcttgttcta	gtgcgccagg	360
cgggacgcct	ctcccgcgat	gcgcctgaag	atgtcggtga	gaaaggagtt	catgtatgccc	420
atggccttgc	accagatgcc	ggtgtcgaaaa	tggaccgcgt	tcagcacctt	gtacacgtag	480
atggagtagc	tctccttgcg	gctgcgcatt	cgcttcttgc	cgtctttctt	ctgggctttg	540
gtgacggctt	tcttggagcc	cttcttggaa	gccggcgca	actttgcagg	ctcaggcatg	600
gccagaccca	agaccgacac	cgacccccga	gaacgcaagc	agagcggtag	gctcggggtc	660
taccggaaac	gactgtgtac	ttacagaggc	tgtgcgcatt	acgctgcgtt	atggttcgcg	720
agtttccgc	ggcgcgcaat	gcgagggaga	cgagattatg	taaatgagtg	gattctggct	780
gagctatcct	attggctatc	gggacaaaat	ttgcttgagc	caatcaaagt	gctccgtgga	840
caatcgccgt	tctgtctata	aaaaggtgaa	gcagcggcgt	tttcggcgac	tttcccgatc	900
gccaggcagg	agtttctctc	ggtactact	atcgctgtca	tgtctggtag	tggcaagcaa	960
ggaggcaagg	cccgcgc当地	ggccaagtgc	cgctcgatccc	gcgcgtggct	tcagttcccg	1020
gtagggcgag	tgcattcgctt	gctgcgc当地	ggcaactacg	cgagcgagt	gggggccccgc	1080
gcgc当地gtct	acatggctgc	ggtcctcgag	tatctgaccg	ccgagatcct	ggagctggcg	1140
ggcaacgcgg	ctcgccgacaa	caagaagacg	cgcatcatcc	ctcgacacct	ccagctggcc	1200
atccgcaacg	acgaggaact	gaacaagctg	ctggccaaag	tcaccatcg	ccagggcgcc	1260
gtcttgccta	acatccaggc	cgtactgctc	cctaagaaga	cgagactca	ccacaaggca	1320
aaggcaagt	gaggctgacg	tccggcccaa	gtgggcccag	cccgccccgc	gtctcgaaagg	1380
ggcacctgtg	aactcaaaag	gctctttca	gagccaccca	cgtttcaaa	taaaagagtt	1440
gttaatgctg	gccactctca	gtccagcgtt	cctcagtagt	gaatagcgaa	cctggagctg	1500
acgggacggg	acgggacggg	acgggacggg	gcggggcgaa	gcggggcgaa	gtgtgtgtgt	1560
gtgcgcgc当地	tcttccatct	ggagcacgta	actgccttgg	ctcttcgatg	agtgggtccc	1620
cagtccctagg	acttcccagg	gcaggtgcag	gcaccaaact	tcctggcgcc	cgccacggc	1680
cgctccacac	agtacacaaac	accagcgccg	cggcagtagc	ccaacgcgc当地	gaagtgttgc	1740
gcgcggagcg	cgcgcttcc					1759

<210> 91  
 <211> 1234  
 <212> DNA  
 <213> Homo sapien

<400> 91	ggtcactctc	tactcaagtt	ctacttatat	aacagcaatg	cagctctttt	cataaaagctg	60
	gctgttgtgt	agtttatgtt	ggggatcag	ttcatggttt	aaaaagttct	gtcaatgcag	120

agaacaagcc	ggtgtgtttt	atggagaggc	tgttaatct	ccactgtgag	acagtaaata	180
tttggctgtt	gcatcatcg	gaagcttatg	atcacagtct	ggcgccatct	ccctcctcgc	240
ctggagtctg	atctgtccc	gccca	gtc	ctccaggaac	ctggccc	300
gcttgcgcgt	gtgccatttc	ctctctccag	aggac	ctgccttagga	ctcatcattg	360
tccccttcct	ggtaagccat	ccccgac	ccaggcagaa	cctgctggct	tctcctcagc	420
actttgcatg	gatttcatgt	cacag	gtgcactgt	gtcgc	ctatgtgtca	480
gcctcccg	ccctaccgt	ggctc	ctcca	gggaggtgt	gacattc	540
cagccctcag	gaatccaggg	agaagataag	gaggcggggc	gggcggaggg	gggtg	600
cacactcaga	acacttcc	ctgcacttac	ttcattctgg	ttttctttt	gggtc	660
tgttttaaa	taaaccc	cctgt	gtt	catggagggc	tgtttcg	720
acagatctgc	tgggtgtct	tatttacaa	gagaagggc	cactcgtgt	tgagc	780
cgagggacag	aggtac	cctgtt	tccc	cttcaa	gtc	840
tccagctgtt	gcctag	ttc	ctgg	tattaa	aaac	900
aatatggccc	atagtcc	cttttacag	gcatttta	cac	ctgg	960
cgc	atgc	g	ctt	ggaa	atgg	1020
tcttaacat	ggttcttct	attc	agtcc	gcca	attaaa	1080
ccatctgg	tggata	acaa	gccc	caca	aaat	1140
ctgggacaac	cacgg	gatct	aaaagg	ggct	aaactag	1200
aaatcatctt	catc	cttat	at	ctgc	actt	1234

<210> 92  
 <211> 730  
 <212> DNA  
 <213> Homo sapien

<400> 92	cagcgtcaga	gagaagaac	tgactgaaac	gtttgagata	tataggaaac	atcaaaaggt	60	
	gataaaat	ttt	ccctagaatc	tccactatct	caaagatgaa	gaaagttctc	ctcctgatca	120
	cagccatctt	gggc	cgtggc	tgtggttc	ccagtctc	aagaccagga	acgagaaaaa	180
	agaagtgtaa	gttac	ttttt	ctctttta	catatc	agtgc	atgcatga	240
	gggtttttt	g	tttcc	ccatatcca	tttgc	ccac	tccat	300
	agat	ttccat	ggtttagac	taat	tttct	attcca	atc	360
	ccc	ttcc	ta	gc	at	ccat	act	420
	ttgaaatt	ga	ccactt	cc	tga	agaat	ca	480

taattgaaat agcacacagc attctctagt caatatctt agtgatcttc ttataataac 540  
atgaaaagcaa atcactaaag atattgacta gagaatgctg tgtgtatattt caatatctt 600  
agtgtatcttc ttataataac atgaaaagcat aaaaaaaaaa agacgaaaaa aaaaggctgg 660  
gggcaccctg ggacaaagcg gtcccgaaaa ggattggttc ccggccaatt ccacaataag 720  
ccgcacaaga 730

<210> 93  
<211> 1159  
<212> DNA  
<213> Homo sapien

<400> 93  
ggggacagat ttctccatc cattatacct ttgagtatataaaaacagcta caatattcca 60  
gggccagtca ctgcattt ctcataacag cgtcagagag aaagaactga ctgaaacgtt 120  
tgagatataat aggaaacatc aaaagggtat aaaaatttccc tagaatctcc actatctcaa 180  
agatgaagaa agttctcctc ctgatcacag ccattttggc agtggctgtt ggtttccag 240  
tctctcaaga ccaggaacga gaaaaaagaa gtgttaaggta cctttctct ttttacata 300  
tcagtgacag cgatgaatta gcttcagggt ttttgcgtt cccttaccca tatccatttc 360  
gcccaattcc accaattcca ttccaagat ttccatgggt tagacgtaat ttccctattc 420  
caatacctga atctgcccc acaactcccc ttccatgcga aaagtaaaca agaaggaaaa 480  
gtcacgataa acctggtcac ctgaaattga aattgagcca cttccctgaa gaatcaaat 540  
tcctgttaat aaaagaaaaa caaatgtaat tgaaatagca cacagcattc tctgtcaat 600  
atcttagtg atcttctta ataaacatga aagaagatca ctaaagatata tgactagaga 660  
atgctgtgtg ctatttcaat tacatttgcgtt ttcttttaat aaacatgaaat tttgatttt 720  
caaggaagtg gctcaatttc aatttcagggt gacctgaaat aaataacaga catatggta 780  
ttaattgcaa tgggtcattt tcttggaaac atatacattt tctgcatttt aatgacaact 840  
atggcttaa aaatataatct agttcaagga ctgggaaacc atctgctaa gatgtgaaaa 900  
gaaagcaaag gtcttttagtg gtaagtagta gctgaaatata tttttccta gaacagtcct 960  
ctgggttcta attaatctt agataagatt aaattataata tattaaatta taaattatta 1020  
tagtagatta gatctataagt ctatagtata gattatattt cctcaattta tctgttaatt 1080  
gacacaccat ccactttgtt ttgtatgtga tgaaatgaca gggccactg ttataggtga 1140  
agcatgaagc ctttaaaat 1159

<210> 94  
<211> 1493

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<400>	94	
ggagcccagc cgtgggattt tcaggtgttt tcatttggtg atcaggactg aacagagaga	60	
actcaccatg gagtttgggc tgagctggct ttttcttgtg gctattttaa aaggtgtcca	120	
gtgtgaggtg cagctgttgg agtctgggg aggcttggta cagcctgggg ggtccctgag	180	
actctccctgt gcagcctctg gattcacctt tagcatctat gccatgagct gggcccgcca	240	
ggctccagg aaggggctgg agtgggtcgc aagtatca gttcagttggta gtagtacata	300	
ctacgcagac tccgtgaagg gccgtttcac catctccaga gacaattcca agaccacgat	360	
gcatctccac atgaacagcc tgagaaccga cgacacggcc gtctactact gtgcgaaacc	420	
gtttccgtat ttgtactact ggggccagg aaccctggc accgtctcga gtggcgatgg	480	
gtccagtggc ggtagcgggg gcgcgtcgac tggcgaagtt gtgttgacgc agtttccagg	540	
gcaccctgtc tctgtctcca gggaaaagag ccaccctctc ctgcaggggcc agtcagagt	600	
cttagcagca gctacttagc ctggtatcag cagagacctg gccaggtcc caggctcctc	660	
gtttatagtg catctgtcg gccaatgtat attccagtca gggccgtgg cagtgggtct	720	
gggacagagt tcactctcac catcagcaga ctggtaacct gaagatttt cagtgtattta	780	
ctgtcaacag ctatggggc tcaccctgacg tggactttcg ccccgccccac caaggtggaa	840	
gtccaaacga actgtggctg caccatctgt cttcatcttc ccgcacatctg atgagcagtt	900	
gaaatctgga actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa	960	
agtacagtgg aaggtggata acgccttacc aatcggttaa ctcggaggag agtgtcacag	1020	
agcaggacag cacaggacag acacccatcag cctcagcgc accctgacgc tgagcaaagc	1080	
agactacgag aaacacaaac tctacgcctg cgaagtccacc catcagggcc tgagctcgcc	1140	
cgtcacaaag agttcaaca ggggagagtg ttagaggag aagtgcggcc acctgctcct	1200	
cagttccagc ctgaccctt cccatcttt ggcctctgac ctttttcca caggggacct	1260	
acccttattc cggccctcca gtcatcttt cacctcaccc ccctctctt cttggcttt	1320	
aattatgcta atgttgagg gagcctgact aaataaaagtg aatctttaaa acacaaaaaa	1380	
aaggaaaaaca aaaaaacaaa aaaaaaaaaa acacgcgggc ggacacccgg ggacaacggg	1440	
gtccccgggg tcacactggc tacccgtcca atttccacca aaacacccgg acc	1493	

&lt;210&gt; 95

&lt;211&gt; 177

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 95

90

Met Asn Ser Gly Lys Arg Arg Leu Pro Trp Arg Leu Arg Ser Gly Val  
1 5 10 15

Pro Ser Pro Pro Gly Leu Leu Ala Pro Ala Pro Ala Pro Cys Ala Pro  
20 25 30

Gly Gly His Arg Arg Ala Pro Gly Pro Arg Arg Val Arg Glu Thr Pro  
35 40 45

Arg Thr Gly Gly Ile Gly Pro Pro Ser Phe Gly Gly Lys Gly  
50 55 60

Gly Trp Lys Glu Glu Gly Ser Gly Val Gly Glu Ser Trp Ser Phe Gly  
65 70 75 80

Ile Phe Ser Pro Gly Gln Ala Val Leu Arg Ala Leu Arg Cys Val Ser  
85 90 95

Lys Cys Trp Glu Asp Ser Ala Gly Lys Gly Leu Arg Thr Arg Pro Ala  
100 105 110

Gly Thr Gly Val Ala Ala Ser Glu Gly Arg Gly Glu Pro Met Ala Ser  
115 120 125

Arg Leu Trp Thr Arg Arg Pro Ser Pro Gly Arg Ser Ala Arg Ser Pro  
130 135 140

Pro Pro Ala Ser Cys Ala Gly Pro Cys Pro Ala Ser Pro Ala Met Val  
145 150 155 160

Pro His Pro Pro Pro Arg Glu Arg Pro Cys Pro Pro Ile Leu His Phe  
165 170 175

Pro

<210> 96  
<211> 55  
<212> PRT  
<213> Homo sapien

<400> 96

Met Gln Asn Ser Thr Ser Ser Gly Leu Cys Val Asn Val Pro Pro Phe  
1 5 10 15

Pro Pro Leu Ser Gly Cys Leu Asn Val Phe Pro Phe Phe His Leu Lys

91

20

25

30

Leu Cys Leu Asp Val Leu His Cys His His Leu Phe Leu Arg Lys Arg  
35 40 45

Cys Val Pro His Pro Asn Pro  
50 55

<210> 97  
<211> 24  
<212> PRT  
<213> Homo sapien

<400> 97

Met Asp His Phe Tyr Leu Leu Ser Asp Thr Tyr Leu Leu Gly Cys Glu  
1 5 10 15

Pro Gln Gly Gly Leu Leu Leu Gly  
20

<210> 98  
<211> 646  
<212> PRT  
<213> Homo sapien

<400> 98

Met Glu Pro Ala Ala Gly Phe Leu Ser Pro Arg Pro Phe Gln Arg Ala  
1 5 10 15

Ala Ala Ala Pro Ala Pro Pro Ala Gly Pro Gly Pro Pro Pro Ser Ala  
20 25 30

Leu Arg Gly Pro Glu Leu Glu Met Leu Ala Gly Leu Pro Thr Ser Asp  
35 40 45

Pro Gly Arg Leu Ile Thr Asp Pro Arg Ser Gly Arg Thr Tyr Leu Lys  
50 55 60

Gly Arg Leu Leu Gly Lys Gly Phe Ala Arg Cys Tyr Glu Ala Thr  
65 70 75 80

Asp Thr Glu Thr Gly Ser Ala Tyr Ala Val Lys Val Ile Pro Gln Ser  
85 90 95

Arg Val Ala Lys Pro His Gln Arg Glu Lys Ile Leu Asn Glu Ile Glu  
100 105 110

92

Leu His Arg Asp Leu Gln His Arg His Ile Val Arg Phe Ser His His  
115 120 125

Phe Glu Asp Ala Asp Asn Ile Tyr Ile Phe Leu Glu Leu Cys Ser Arg  
130 135 140

Lys Ser Leu Ala His Ile Trp Lys Ala Arg His Thr Leu Leu Glu Pro  
145 150 155 160

Glu Val Arg Tyr Tyr Leu Arg Gln Ile Leu Ser Gly Leu Lys Tyr Leu  
165 170 175

His Gln Arg Gly Ile Leu His Arg Asp Leu Lys Leu Gly Asn Phe Phe  
180 185 190

Ile Thr Glu Asn Met Glu Leu Lys Val Gly Asp Phe Gly Leu Ala Ala  
195 200 205

Arg Leu Glu Pro Pro Glu Gln Arg Lys Lys Thr Ile Cys Gly Thr Pro  
210 215 220

Asn Tyr Val Ala Pro Glu Val Leu Leu Arg Gln Gly His Gly Pro Glu  
225 230 235 240

Ala Asp Val Trp Ser Leu Gly Cys Val Met Tyr Thr Leu Leu Cys Gly  
245 250 255

Ser Pro Pro Phe Glu Thr Ala Asp Leu Lys Glu Thr Tyr Arg Cys Ile  
260 265 270

Lys Gln Val His Tyr Thr Leu Pro Ala Ser Leu Ser Leu Pro Ala Arg  
275 280 285

Gln Leu Leu Ala Ala Ile Leu Arg Ala Ser Pro Arg Asp Arg Pro Ser  
290 295 300

Ile Asp Gln Ile Leu Arg His Asp Phe Phe Thr Lys Gly Tyr Thr Pro  
305 310 315 320

Asp Arg Leu Pro Ile Ser Ser Cys Val Thr Val Pro Asp Leu Thr Pro  
325 330 335

Pro Asn Pro Ala Arg Ser Leu Phe Ala Lys Val Thr Lys Ser Leu Phe  
340 345 350

Gly Arg Lys Lys Lys Ser Lys Asn His Ala Gln Glu Arg Asp Glu Val

93

355

360

365

Ser Gly Leu Val Ser Gly Leu Met Arg Thr Ser Val Gly His Gln Asp  
370 375 380

Ala Arg Pro Glu Ala Pro Ala Ala Ser Gly Pro Ala Pro Val Ser Leu  
385 390 395 400

Val Glu Thr Ala Pro Glu Asp Ser Ser Pro Arg Gly Thr Leu Ala Ser  
405 410 415

Ser Gly Asp Gly Phe Glu Glu Gly Leu Thr Val Ala Thr Val Val Glu  
420 425 430

Ser Ala Leu Cys Ala Leu Arg Asn Cys Ile Ala Phe Met Pro Pro Ala  
435 440 445

Glu Gln Asn Pro Ala Pro Leu Ala Gln Pro Glu Pro Leu Val Trp Val  
450 455 460

Ser Lys Trp Val Asp Tyr Ser Asn Lys Phe Gly Phe Gly Tyr Gln Leu  
465 470 475 480

Ser Ser Arg Arg Val Ala Val Leu Phe Asn Asp Gly Thr His Met Ala  
485 490 495

Leu Ser Ala Asn Arg Lys Thr Val His Tyr Asn Pro Thr Ser Thr Lys  
500 505 510

His Phe Ser Phe Ser Val Gly Ala Val Pro Arg Ala Leu Gln Pro Gln  
515 520 525

Leu Gly Ile Leu Arg Tyr Phe Ala Ser Tyr Met Glu Gln His Leu Met  
530 535 540

Lys Gly Gly Asp Leu Pro Ser Val Glu Glu Val Glu Val Pro Ala Pro  
545 550 555 560

Pro Leu Leu Leu Gln Trp Val Lys Thr Asp Gln Ala Leu Leu Met Leu  
565 570 575

Phe Ser Asp Gly Thr Val Gln Val Asn Phe Tyr Gly Asp His Thr Lys  
580 585 590

Leu Ile Leu Ser Gly Trp Glu Pro Leu Leu Val Thr Phe Val Ala Arg  
595 600 605

Asn Arg Ser Ala Cys Thr Tyr Leu Ala Ser His Leu Arg Gln Leu Gly  
610 615 620

Cys Ser Pro Asp Leu Arg Gln Arg Leu Arg Tyr Ala Leu Arg Leu Leu  
625 630 635 640

Arg Asp Arg Ser Pro Ala  
645

<210> 99  
<211> 99  
<212> PRT  
<213> Homo sapien

<400> 99

Met Leu Thr Ser Pro Ser Thr Tyr Val Ile Gln Glu Asn Gly Ser Leu  
1 5 10 15

Val Glu Ile Arg Asn Ile Leu Gly Glu Lys Tyr Ile Arg Arg Val Arg  
20 25 30

Met Arg Pro Gly Val Ala Cys Ser Val Ser Gln Ala Gln Lys Asp Glu  
35 40 45

Leu Ile Leu Glu Gly Asn Asp Ile Glu Leu Val Ser Asn Ser Ala Cys  
50 55 60

Phe Gly Cys Gln Gln Met Pro Gln Ser Val Lys Asn Lys Asp Ile Arg  
65 70 75 80

Lys Phe Leu Asp Gly Ile Tyr Val Ser Glu Lys Gly Thr Val Gln Gln  
85 90 95

Ala Asp Glu

<210> 100  
<211> 220  
<212> PRT  
<213> Homo sapien

<400> 100

Met Lys Thr Ile Leu Ser Asn Gln Thr Val Asp Ile Pro Glu Asn Gly  
1 5 10 15

Met Arg Leu Asp Val Phe Tyr Leu His Leu Tyr Cys Thr Phe Gln Ala

95

20

25

30

Leu Cys Gly Leu Thr Ser Val Phe Ser Leu Leu Val Asp Ile Thr Leu  
35 40 45

Lys Gly Arg Thr Val Ile Val Lys Gly Pro Arg Gly Thr Leu Arg Arg  
50 55 60

Asp Phe Asn His Ile Asn Val Glu Leu Ser Leu Leu Gly Lys Lys Lys  
65 70 75 80

Lys Arg Leu Arg Val Asp Lys Trp Trp Gly Asn Arg Lys Glu Leu Ala  
85 90 95

Thr Val Arg Thr Ile Cys Ser His Val Gln Asn Met Ile Lys Gly Val  
100 105 110

Thr Leu Gly Phe Arg Tyr Lys Met Arg Ser Val Tyr Ala His Phe Pro  
115 120 125

Ile Asn Val Val Ile Gln Glu Asn Gly Ser Leu Val Glu Ile Arg Asn  
130 135 140

Phe Leu Gly Glu Lys Tyr Ile Arg Arg Val Arg Met Arg Pro Gly Val  
145 150 155 160

Ala Cys Ser Val Ser Gln Ala Gln Lys Asp Glu Leu Ile Leu Glu Gly  
165 170 175

Asn Asp Ile Glu Leu Val Ser Asn Ser Ala Ala Leu Ile Gln Gln Ala  
180 185 190

Thr Thr Val Lys Asn Lys Asp Ile Arg Lys Phe Leu Asp Gly Ile Tyr  
195 200 205

Val Ser Glu Lys Gly Thr Val Gln Gln Ala Asp Glu  
210 215 220

<210> 101

<211> 47

<212> PRT

<213> Homo sapien

<400> 101

Met Arg Trp His Thr Tyr Leu Cys Cys Leu Lys Val Thr Ile Met Leu  
1 5 10 15

Pro Tyr Gln Ala Glu Asn Val Thr Thr Ile Trp Arg Phe Arg Arg Val  
20 25 30

Phe Leu Ser Glu Ser Val Met Asn Thr Leu Val Gly Trp Ile Gln  
35 40 45

<210> 102

<211> 51

<212> PRT

<213> Homo sapien

<400> 102

Met Ser Ser His Lys Thr Phe Arg Ile Lys Arg Phe Leu Ala Lys Lys  
1 5 10 15

Gln Lys Gln Asn Arg Pro Ile Pro Gln Trp Ile Arg Met Lys Thr Gly  
20 25 30

Asn Lys Ile Arg Tyr Asn Ser Lys Arg Arg His Trp Arg Arg Thr Lys  
35 40 45

Leu Gly Leu  
50

<210> 103

<211> 53

<212> PRT

<213> Homo sapien

<400> 103

Met Glu Arg Val Leu Glu Lys Gln Glu Lys Lys Ser Cys Leu Lys Pro  
1 5 10 15

His Val Tyr Cys Arg His Arg Arg Glu Trp Arg His Leu Ser Ile Leu  
20 25 30

Phe Ser Ile Ser Thr Ala Pro Gln Asn Thr Tyr Ile Leu Phe Phe Phe  
35 40 45

Phe Ser Glu Met Ser  
50

<210> 104

<211> 131

<212> PRT

<213> Homo sapien

<400> 104

Met Arg Val Ser Glu Arg Ala Leu Lys Asn Val Ala Cys Gln Gln His  
1 5 10 15

Met Asp Ser Leu Phe Arg Val Cys Ile Tyr Pro Ala Asp Thr Pro Ile  
20 25 30

Pro Pro Ser Leu Pro Pro Arg Ala Ser Asp Phe Leu Phe His Pro Ala  
35 40 45

Ala Tyr Tyr Trp Gln Gly Met Ala Gly Val Asn Leu Gly Ser Val Tyr  
50 55 60

His Gln Gly Lys Leu Pro Ser Leu Leu Gln Ser Leu Trp Lys Gly Thr  
65 70 75 80

Phe Phe Arg Val Gln His Val Pro Met His Ser Gln Val Pro Lys Val  
85 90 95

Thr Tyr Thr Tyr Ile Val Asn Ile Val Pro Thr Ala Leu Gln Thr Phe  
100 105 110

Ile Trp Pro Leu Ala Val His Thr Ser Gln Pro Ile His Val Phe Met  
115 120 125

Met Met Phe  
130

<210> 105  
<211> 117  
<212> PRT  
<213> Homo sapien

<400> 105

Met Ser Ser Phe Gln Gly Phe Ile Phe Gly Gly Lys Lys Ile Pro Gln  
1 5 10 15

Asp Ala Gly Cys Pro Ala Ser His Asn Gly Tyr Ala Pro Ile Glu Thr  
20 25 30

Ser Ser Gly Arg Val Thr Lys Leu Lys Arg Lys Gln Phe Gln Ala Glu  
35 40 45

Gly His Lys Leu Arg Ala Glu Ser Leu Leu Leu Thr Ala Ile Gln Ala  
50 55 60

Gln Gly Leu Cys Gly Ala Gly Phe Leu Lys Ala Gly Leu Tyr Leu Gly

98

65

70

75

80

Arg Arg Glu Arg Thr Arg Gly Leu Asp Ala Gly Trp Arg Phe Cys Asp  
85 90 95

Leu Leu Cys Tyr Lys Phe Lys Asn Lys Thr Cys Trp Ile Arg Ser Phe  
100 105 110

Ser Tyr Leu Leu Lys  
115

<210> 106

<211> 93

<212> PRT

<213> Homo sapien

<400> 106

Met Pro Gly Val Thr Val Lys Asp Val Asn Gln Gln Glu Phe Val Arg  
1 5 10 15

Ala Leu Ala Ala Phe Leu Lys Lys Ser Gly Glu Ala Glu Ser Pro Arg  
20 25 30

Met Gly Gly Ile Pro Phe Lys Leu Ala Lys Ala Gln Arg Ser Leu Leu  
35 40 45

Pro Thr Met Arg Thr Gly Ser Thr Arg Gly Ala Ala Phe Gln Gln Arg  
50 55 60

Arg Ala Thr Cys Tyr Leu Pro Gly Val Gly Ala Gly Gly Trp Ala Ser  
65 70 75 80

Ile Glu Pro Lys Asp Ser Ile Gly Gly Glu Arg Ser Glu  
85 90

<210> 107

<211> 148

<212> PRT

<213> Homo sapien

<400> 107

Met Leu Leu Val Gly Ser Cys His Leu Ser Gly Asp Ser Val Gln Ile  
1 5 10 15

Ser Leu Ser Leu Arg Cys Gln Phe Ala Ala Ala Ile Leu Val Leu Phe  
20 25 30

99

His His Phe Gln Pro Leu Gln Gly Leu Glu Asp Pro Ala Gly His Thr  
35 40 45

Leu Gly Ala Ser Ala Glu Val Ala Gly His Asp Ala Val Ser Leu Thr  
50 55 60

Ser Pro Ile Asp Leu Gly His Gly Ala Asn Pro Ser Ala Thr Pro Glu  
65 70 75 80

Val Gln Val Pro Arg Cys Gly Ser Ser Arg Val Glu Pro Val Leu  
85 90 95

Ile Val Gly Ser Lys Leu Phe Val Leu Gly Gln Leu Asp Gly Ile His  
100 105 110

Pro Phe Gly Asp Phe Gln Leu Pro Gly Leu Phe Glu Glu Gly Cys Gln  
115 120 125

Ser Ser Asp Glu Leu Leu Val His Val Phe Tyr Ser Asn Ser Arg  
130 135 140

His Arg Ala Ala  
145

<210> 108  
<211> 172  
<212> PRT  
<213> Homo sapien

<400> 108  
Met Val Cys Gly Gly Phe Ala Cys Ser Ser Leu Arg Val Val Gly Val  
1 5 10 15

Val Ile Ala Val Gly Ile Phe Leu Phe Leu Ile Ala Leu Val Gly Leu  
20 25 30

Ile Gly Ala Val Lys His His Gln Val Leu Leu Phe Phe Tyr Met Ile  
35 40 45

Ile Leu Leu Leu Val Phe Ile Val Gln Phe Ser Val Ser Cys Ala Cys  
50 55 60

Leu Ala Leu Asn Gln Glu Gln Gln Gly Gln Leu Leu Glu Val Gly Trp  
65 70 75 80

Asn Asn Thr Ala Ser Ala Arg Asn Asp Ile Gln Arg Asn Leu Asn Cys  
85 90 95

100

Cys Gly Phe Arg Ser Val Asn Pro Asn Asp Thr Cys Leu Ala Ser Cys  
100 105 110

Val Lys Ser Asp His Ser Cys Ser Pro Cys Ala Pro Ile Ile Gly Glu  
115 120 125

Tyr Ala Gly Glu Val Leu Arg Phe Val Gly Gly Ile Gly Leu Phe Phe  
130 135 140

Ser Phe Thr Glu Ile Leu Gly Val Trp Leu Thr Tyr Arg Tyr Arg Asn  
145 150 155 160

Gln Lys Asp Pro Arg Ala Asn Pro Ser Ala Phe Leu  
165 170

<210> 109

<211> 55

<212> PRT

<213> Homo sapien

<400> 109

Met Asn Phe Asp Tyr Ser Val Asn Tyr Trp Asn Val Ser Ser Phe Asn  
1 5 10 15

Phe Lys Asn Asn Tyr Phe Thr Ser Ser Asp Trp Gly Phe Pro Glu Ile  
20 25 30

Cys Glu Glu Gln Arg Arg Pro Pro Ala Thr Gln His His His Asp Gly  
35 40 45

Ala Leu Thr Gly Ser Glu Ser  
50 55

<210> 110

<211> 125

<212> PRT

<213> Homo sapien

<400> 110

Met Gln Ala Leu Pro Gln Val Glu Lys Arg Arg Leu Arg Leu Pro Arg  
1 5 10 15

Glu Val Gln Cys Pro Ala Leu Leu Arg Arg Met Leu Leu Ile Pro Leu  
20 25 30

Trp Lys Ile Pro Ala Pro Thr Thr Lys Ser Cys Arg Glu Thr Phe

101

35

40

45

Leu Lys Trp Leu Ser Val Ser Ala Ala Glu Arg Thr Thr Gly Ser Trp  
50 55 60

Thr Ser Phe Gln Pro Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro  
65 70 75 80

Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg  
85 90 95

Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser  
100 105 110

Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
115 120 125

<210> 111  
<211> 1256  
<212> PRT  
<213> Homo sapien

<400> 111

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60

Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80

Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
85 90 95

Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
100 105 110

Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro  
115 120 125

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
130 135 140

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
145 150 155 160

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
165 170 175

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala  
180 185 190

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
195 200 205

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
210 215 220

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
225 230 235 240

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
245 250 255

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
260 265 270

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
275 280 285

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
290 295 300

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
305 310 315 320

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
325 330 335

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
340 345 350

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
355 360 365

103

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
370                   375                   380

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
385                   390                   395                   400

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
405                   410                   415

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
420                   425                   430

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
435                   440                   445

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
450                   455                   460

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
465                   470                   475                   480

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
485                   490                   495

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
500                   505                   510

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
515                   520                   525

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
530                   535                   540

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
545                   550                   555                   560

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
565                   570                   575

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
580                   585                   590

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
595                   600                   605

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr

104

610

615

620

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
625                       630                       635                       640

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
645                       650                       655

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
660                       665                       670

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
675                       680                       685

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
690                       695                       700

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
705                       710                       715                       720

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
725                       730                       735

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
740                       745                       750

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
755                       760                       765

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
770                       775                       780

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
785                       790                       795                       800

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
805                       810                       815

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
820                       825                       830

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
835                       840                       845

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
850                       855                       860

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
865 870 875 880

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Val His  
885 890 895

Gly Val Thr Ser Ala Pro Asp Ser Arg Ser Gly Ser Gly Phe Leu Pro  
900 905 910

Pro Pro Ala Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala  
915 920 925

Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp  
930 935 940

Asn Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr  
945 950 955 960

Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn  
965 970 975

Gly Thr Ser Ala Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro  
980 985 990

Phe Ser Ile Pro Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser  
995 1000 1005

His Ser Thr Lys Thr Asp Ala Ser Ser Thr His His Ser Thr Val  
1010 1015 1020

Pro Pro Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln Leu Ser  
1025 1030 1035

Thr Gly Val Ser Phe Phe Leu Ser Phe His Ile Ser Asn Leu  
1040 1045 1050

Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln  
1055 1060 1065

Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys  
1070 1075 1080

Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly  
1085 1090 1095

Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile  
1100 1105 1110

Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu  
1115 1120 1125

Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser  
1130 1135 1140

Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro  
1145 1150 1155

Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala  
1160 1165 1170

Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg  
1175 1180 1185

Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr  
1190 1195 1200

Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg  
1205 1210 1215

Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val  
1220 1225 1230

Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala  
1235 1240 1245

Val Ala Ala Thr Ser Ala Asn Leu  
1250 1255

<210> 112  
<211> 728  
<212> PRT  
<213> Homo sapien

<400> 112

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser

107

35

40

45

Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60

Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80

Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
85 90 95

Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
100 105 110

Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro  
115 120 125

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
130 135 140

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Pro Ala His Gly Val Thr  
145 150 155 160

Ser Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala  
165 170 175

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
180 185 190

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
195 200 205

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
210 215 220

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
225 230 235 240

Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
245 250 255

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
260 265 270

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
275 280 285

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
290                   295                   300

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
305                   310                   315                   320

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
325                   330                   335

Met Val Ser Ile Gly Leu Ser Phe Pro Ser Ser Pro Glu Ala Ala Ile  
340                   345                   350

Arg Thr Val His Thr Leu Cys Ile Lys Pro Glu Ser Phe Pro Ser His  
355                   360                   365

Pro Ser Phe Cys Arg Phe Ile Asn Lys Gly Val Phe Trp Ala Ser Pro  
370                   375                   380

Ile Leu Ser Ser Gly Thr Val Leu Gly Val Asp Pro Val Trp Trp Leu  
385                   390                   395                   400

Glu Gly Trp Val Val Val Met Thr Val Gly Gly Thr Gly Arg Thr Tyr  
405                   410                   415

Gly Trp Gly Lys Ser Arg Glu Pro Glu Leu Gly Pro Val Ala Glu Val  
420                   425                   430

Pro Ile Phe Pro Val Thr Arg Pro Gly Ser Val Val Val Gln Leu Thr  
435                   440                   445

Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln  
450                   455                   460

Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile  
465                   470                   475                   480

Ser Asp Val Ser Gly Glu Ala Thr Ser Leu Ala Ala Ala Gln His His  
485                   490                   495

Ala Gly Ala Leu Ser Phe Gln Cys Leu Gly Pro Arg Ser Phe Leu Ser  
500                   505                   510

Ala Gly Ser Gly Arg Gly Ala Ser Ser Gly Arg Leu Pro Cys Pro Leu  
515                   520                   525

109

Leu Phe Leu Leu Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser  
530 535 540

Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys  
545 550 555 560

Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Val Ser Ala  
565 570 575

Val Pro Gly Pro Asp Gln Ser Pro Pro Val Glu Gly Ser Ser Met Ala  
580 585 590

Cys His Asn Leu Leu Ser Pro Gln Ala Val Cys Gln Cys Arg Arg Lys  
595 600 605

Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro  
610 615 620

Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro  
625 630 635 640

Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Arg Leu Ala Pro Gln  
645 650 655

Ala Arg Gly Ser Arg Gly Phe Gly Trp Ala Arg Ile Leu Lys Gly Val  
660 665 670

Leu Gly Lys Pro Lys Glu Leu Gly Arg Gly Glu Lys Trp Arg Glu Val  
675 680 685

Ser Arg Gly Gly Pro Gly Lys Asp Glu Gly Gln Arg Ser Glu Glu Phe  
690 695 700

Trp Gly Thr Gly Leu Gly Gly Asp Tyr Gly Arg Lys Gly Pro Ser Lys  
705 710 715 720

Gly Ser Gly Pro Thr Ala Arg Ile  
725

<210> 113  
<211> 524  
<212> PRT  
<213> Homo sapien

<400> 113

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr

110  
1           5           10           15

Val Leu Thr Ala Thr Thr Ala Pro Thr Pro Ala Thr Val Val Thr Gly  
20                         25                         30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35                         40                         45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50                         55                         60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65                         70                         75                         80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85                         90                         95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100                         105                         110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115                         120                         125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130                         135                         140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145                         150                         155                         160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala  
165                         170                         175

Pro Gly Ser Thr Ala Pro Ala Ala His Gly Val Thr Ser Ala Pro Asp  
180                         185                         190

Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr  
195                         200                         205

Ser Ala Pro Asp Asn Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val  
210                         215                         220

His Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr  
225                         230                         235                         240

Leu Val His Asn Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser  
245                         250                         255

111

Lys Ser Thr Pro Phe Ser Ile Pro Ser His His Ser Asp Thr Pro Thr  
260 265 270

Thr Leu Ala Ser His Ser Thr Lys Thr Asp Ala Ser Ser Thr His His  
275 280 285

Ser Thr Val Pro Pro Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln  
290 295 300

Leu Ser Thr Gly Val Ser Phe Phe Leu Ser Phe His Ile Ser Asn  
305 310 315 320

Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln  
325 330 335

Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln  
340 345 350

Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val  
355 360 365

Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His  
370 375 380

Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg  
385 390 395 400

Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro  
405 410 415

Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu  
420 425 430

Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile  
435 440 445

Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp  
450 455 460

Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr  
465 470 475 480

Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser  
485 490 495

Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr  
500 505 510

Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
515 520

<210> 114  
<211> 515  
<212> PRT  
<213> Homo sapien

<400> 114

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60

Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80

Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
85 90 95

Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
100 105 110

Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro  
115 120 125

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
130 135 140

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
145 150 155 160

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Ala Ala His  
165 170 175

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala

113

180

185

190

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu  
195 200 205

Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser  
210 215 220

Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg  
225 230 235 240

Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser  
245 250 255

His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr  
260 265 270

Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser  
275 280 285

Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe  
290 295 300

Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp  
305 310 315 320

Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met  
325 330 335

Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile  
340 345 350

Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg  
355 360 365

Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr  
370 375 380

Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser  
385 390 395 400

Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val  
405 410 415

Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala  
420 425 430

Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg  
435 440 445

Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His  
450 455 460

Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro  
465 470 475 480

Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn  
485 490 495

Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser  
500 505 510

Ala Asn Leu  
515

<210> 115  
<211> 109  
<212> PRT  
<213> Homo sapien

<400> 115

Met Leu Glu Arg Arg Pro Pro Ala Val Arg Arg Pro Gly Leu Thr Ala  
1 5 10 15

Pro Ala Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
20 25 30

Gly Ser Thr Ala Pro Ala Ala His Gly Val Thr Ser Ala Pro Asp Thr  
35 40 45

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Phe  
50 55 60

Val Pro Arg Thr Ser Gly Arg Arg Leu Ala Leu Phe Leu Val Tyr Val  
65 70 75 80

Phe Arg Val Glu Asp Val Val Gln Thr Arg Leu Asp Thr Leu Arg Ile  
85 90 95

Ala Lys Tyr Ile Asp Gly Ser Tyr Ala Val Ser Val Cys  
100 105

115

<210> 116  
<211> 174  
<212> PRT  
<213> Homo sapien

<220>  
<221> MISC\_FEATURE  
<222> (167)..(167)  
<223> X= any amino acid

<400> 116

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Thr Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Arg Pro  
130 135 140

Ser Cys Gly Ser Gly Leu Gly Thr Ala Cys Val Pro Gly Leu Gln Leu  
145 150 155 160

Leu Leu Val Gly Ala His Xaa Thr Gln Leu Leu Thr Tyr Asp  
165 170

<210> 117  
<211> 475  
<212> PRT  
<213> Homo sapien

&lt;400&gt; 117

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60

Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80

Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
85 90 95

Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
100 105 110

Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro  
115 120 125

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
130 135 140

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
145 150 155 160

Ala Pro Asp Asn Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val His  
165 170 175

Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu  
180 185 190

Val His Asn Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys  
195 200 205

Ser Thr Pro Phe Ser Ile Pro Ser His His Ser Asp Thr Pro Thr Thr  
210 215 220

Leu Ala Ser His Ser Thr Lys Thr Asp Ala Ser Ser Thr His His Ser  
225 230 235 240

Thr Val Pro Pro Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln Leu  
245 250 255

Ser Thr Gly Val Ser Phe Phe Leu Ser Phe His Ile Ser Asn Leu  
260 265 270

Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu  
275 280 285

Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly  
290 295 300

Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val  
305 310 315 320

Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp  
325 330 335

Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr  
340 345 350

Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe  
355 360 365

Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu  
370 375 380

Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala  
385 390 395 400

Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile  
405 410 415

Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr  
420 425 430

His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro  
435 440 445

Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr  
450 455 460

Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
465 470 475

&lt;210&gt; 118

&lt;211&gt; 231

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 118

Met Cys Pro Leu Ala Val Pro Ile Val Ala Pro Met Arg Arg Phe Leu  
1 5 10 15

Gln Val Met Val Ala Ala Ala Ser Leu Thr Gln Thr Gln Gln Trp Gln  
20 25 30

Pro Leu Leu Pro Thr Cys Arg Gly Thr Ser Pro Ala Glu Leu Ser Gly  
35 40 45

Gln Pro Val Pro Phe His Ser Thr Gln Val Leu Gln Gly Gln Ser Pro  
50 55 60

Cys Thr Leu Phe Gly Leu Val Ser Trp Glu Phe Arg Trp Ala Ala His  
65 70 75 80

Ser Leu Leu Gln Arg Pro His Asp Tyr Phe Arg Lys Phe Glu Pro His  
85 90 95

Leu Tyr Ser Leu Asp Ser Asn Ser Asp Asp Val Asp Ser Leu Thr Asp  
100 105 110

Glu Glu Ile Leu Ser Lys Tyr Gln Leu Gly Met Leu His Phe Ser Thr  
115 120 125

Gln Tyr Asp Leu Leu His Asn His Leu Thr Val Arg Val Ile Glu Ala  
130 135 140

Arg Asp Leu Pro Pro Ile Ser His Asp Gly Ser Arg Gln Asp Met  
145 150 155 160

Ala His Ser Asn Pro Tyr Val Lys Ile Cys Leu Leu Pro Asp Gln Lys  
165 170 175

Asn Ser Lys Gln Thr Gly Val Lys Arg Lys Thr Gln Lys Pro Val Phe  
180 185 190

Glu Glu Arg Tyr Thr Phe Glu Ile Pro Phe Leu Glu Ala Gln Arg Arg  
195 200 205

Thr Leu Leu Leu Thr Val Val Asp Phe Asp Lys Phe Ser Arg His Cys

119

210

215

220

Val Ile Gly Lys Val Ser Val  
225 230

<210> 119  
<211> 107  
<212> PRT  
<213> Homo sapien

&lt;400&gt; 119

Met Val Ala Ala Ala Ser Leu Thr Gln Thr Gln Gln Trp Gln Pro Leu  
1 5 10 15

Leu Pro Thr Cys Arg Gly Thr Ser Pro Ala Glu Leu Ser Gly Gln Pro  
20 25 30

Val Pro Phe His Ser Thr Gln Val Leu Gln Gly Gln Ser Pro Cys Thr  
35 40 45

Leu Phe Gly Leu Val Ser Trp Glu Phe Arg Trp Ala Ala His Ser Leu  
50 55 60

Leu Gln Arg Pro His Gln Phe Leu Gly His Phe Ser Val Cys Gly Ser  
65 70 75 80

Ser Cys Gly Pro Leu Arg Ala His Ala Trp Glu Val Leu Trp Trp Gly  
85 90 95

Leu Pro Gly Gly Leu Ala Gln Arg Ala Leu Arg  
100 105

<210> 120  
<211> 484  
<212> PRT  
<213> Homo sapien

&lt;400&gt; 120

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

120

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu

121

290

295

300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe  
325 330 335

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
340 345 350

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
355 360 365

Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly  
370 375 380

Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val  
385 390 395 400

Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg  
405 410 415

Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr  
420 425 430

His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val  
435 440 445

Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly  
450 455 460

Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr  
465 470 475 480

Ser Ala Asn Leu

<210> 121  
<211> 463  
<212> PRT  
<213> Homo sapien  
  
<400> 121

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

122

Val Leu Thr Gly Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser  
20 25 30

Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val  
35 40 45

Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln  
50 55 60

Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala  
65 70 75 80

Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu  
85 90 95

Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn  
100 105 110

Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
115 120 125

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
130 135 140

Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu Gly Ser Thr Ala  
145 150 155 160

Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser  
165 170 175

Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg Ala Thr Thr Thr  
180 185 190

Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser His His Ser Asp  
195 200 205

Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr Asp Ala Ser Ser  
210 215 220

Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser Asn His Ser Thr  
225 230 235 240

Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe Leu Ser Phe His  
245 250 255

123

Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp  
260 265 270

Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile  
275 280 285

Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro  
290 295 300

Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile  
305 310 315 320

Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala  
325 330 335

Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val  
340 345 350

Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly  
355 360 365

Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val  
370 375 380

Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly  
385 390 395 400

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu  
405 410 415

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr  
420 425 430

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser  
435 440 445

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
450 455 460

<210> 122  
<211> 524  
<212> PRT  
<213> Homo sapien

<400> 122

Met Gly Arg Glu Lys Glu Ala Ala Ala Gly Lys Glu Ala Ala Asn Pro  
1 5 10 15

Gly Val Thr Glu Ala Ala His Ser Pro Val Leu Leu Val Leu Phe Leu  
20 25 30

Trp Trp Pro Glu Leu Ile Phe Ser Ser Cys Ser Tyr Phe Ser Phe Ile  
35 40 45

Lys Thr Gln Pro Tyr Asp Phe Asn Phe Phe Thr Ala Thr Thr Ala Pro  
50 55 60

Lys Pro Ala Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro  
65 70 75 80

Gly Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser  
85 90 95

Ser Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser  
100 105 110

His Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr  
115 120 125

Leu Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly  
130 135 140

Gln Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr  
145 150 155 160

Thr Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala  
165 170 175

Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp  
180 185 190

Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr  
195 200 205

Ser Ala Pro Asp Asn Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val  
210 215 220

His Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr  
225 230 235 240

Leu Val His Asn Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser  
245 250 255

125

Lys Ser Thr Pro Phe Ser Ile Pro Ser His His Ser Asp Thr Pro Thr  
260 265 270

Thr Leu Ala Ser His Ser Thr Lys Thr Asp Ala Ser Ser Thr His His  
275 280 285

Ser Thr Val Pro Pro Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln  
290 295 300

Leu Ser Thr Gly Val Ser Phe Phe Leu Ser Phe His Ile Ser Asn  
305 310 315 320

Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln  
325 330 335

Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln  
340 345 350

Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val  
355 360 365

Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His  
370 375 380

Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg  
385 390 395 400

Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro  
405 410 415

Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu  
420 425 430

Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile  
435 440 445

Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp  
450 455 460

Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr  
465 470 475 480

Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser  
485 490 495

126

Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr  
500 505 510

Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
515 520

<210> 123  
<211> 435  
<212> PRT  
<213> Homo sapien

<400> 123

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60

Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80

Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
85 90 95

Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
100 105 110

Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu  
115 120 125

Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser  
130 135 140

Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg  
145 150 155 160

Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser  
165 170 175

His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr  
180 185 190

Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser  
195 200 205

Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe  
210 215 220

Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp  
225 230 235 240

Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met  
245 250 255

Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile  
260 265 270

Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg  
275 280 285

Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr  
290 295 300

Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser  
305 310 315 320

Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val  
325 330 335

Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala  
340 345 350

Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg  
355 360 365

Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His  
370 375 380

Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro  
385 390 395 400

Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn  
405 410 415

Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Thr Ser  
420 425 430

Ala Asn Leu  
435

<210> 124  
<211> 273  
<212> PRT  
<213> Homo sapien

<400> 124

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Leu Ser Thr Gly Val Ser Phe Phe Leu Ser  
50 55 60

Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser  
65 70 75 80

Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu  
85 90 95

Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe  
100 105 110

Arg Pro Gly Ser Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly  
115 120 125

Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr  
130 135 140

Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser  
145 150 155 160

Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly  
165 170 175

Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala  
180 185 190

Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn

129

195

200

205

Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met  
210 215 220

Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser  
225 230 235 240

Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly  
245 250 255

Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn  
260 265 270

Leu

<210> 125  
<211> 350  
<212> PRT  
<213> *Homo sapien*

<400> 125

Met	Thr	Pro	Gly	Thr	Gln	Ser	Pro	Phe	Phe	Leu	Leu	Leu	Leu	Leu	Leu	Thr
1					5				10						15	

Val	Leu	Thr	Ala	Thr	Thr	Ala	Pro	Lys	Pro	Ala	Thr	Val	Val	Thr	Gly
20							25						30		

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
           35                  40                  45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met	Thr	Ser	Ser	Val	Leu	Ser	Ser	His	Ser	Pro	Gly	Ser	Gly	Ser	Ser
65					70					75					80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
 115 120 125

130

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Arg Tyr Ser Ser Gly Cys Gly Pro Ser Val Val Val Gly  
325 330 335

Gly Trp Val Val Val Met Thr Val Gly Arg Asp Trp Cys Thr  
340 345 350

<210> 126

<211> 316

<212> PRT

<213> Homo sapien

&lt;400&gt; 126

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Val Ser Ile Gly Leu Ser Phe Pro Met Leu Pro  
305 310 315

<210> 127  
<211> 230  
<212> PRT  
<213> Homo sapien

<400> 127

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Ile Pro Ala Pro Thr Thr Lys Ser Cys Arg  
50 55 60

Glu Thr Phe Leu Lys Trp Pro Gly Ser Val Val Gln Leu Thr Leu  
65 70 75 80

Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe  
85 90 95

Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser  
100 105 110

Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly  
115 120 125

133

Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val  
130 135 140

Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln  
145 150 155 160

Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp  
165 170 175

Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg  
180 185 190

Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser  
195 200 205

Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala  
210 215 220

Ala Thr Ser Ala Asn Leu  
225 230

<210> 128

<211> 614

<212> PRT

<213> Homo sapien

<400> 128

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Arg Pro Gly Ser Val Val Gln Leu Thr Leu Ala Phe  
325 330 335

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
340 345 350

135

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
355 360 365

Ser Val Leu Leu Ile Gly Gly Glu Arg Arg Tyr Arg Ala Met Val  
370 375 380

Ser Ala Thr Gly Ile Ser Leu Gly Ala Met Ala Gly Lys Gly Gly  
385 390 395 400

Val Ser Glu Trp Trp Leu Gly Ile Glu Asn Gly Val Leu Leu Ala  
405 410 415

Gly Val Val Val Ala Leu Ala Glu Val Pro Leu Cys Thr Arg Val Glu  
420 425 430

Ala Glu Pro Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu  
435 440 445

Thr Ser Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser  
450 455 460

Phe Phe Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser  
465 470 475 480

Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile  
485 490 495

Ser Glu Asp Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly  
500 505 510

Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val  
515 520 525

Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln  
530 535 540

Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp  
545 550 555 560

Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg  
565 570 575

Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser  
580 585 590

136

Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala  
595 600 605

Ala Thr Ser Ala Asn Leu  
610

<210> 129  
<211> 372  
<212> PRT  
<213> Homo sapien

<400> 129

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Trp Gly Ala Arg Leu Gly His Arg Ala Ala Gly Ala Gly Leu Cys  
305 310 315 320

Ser Gly Cys Ala Gly His Cys Leu Ser His Cys Leu Gly Cys Leu Ser  
325 330 335

Val Pro Pro Lys Glu Leu Arg Ala Ala Gly His Leu Ser Ser Pro Gly  
340 345 350

Tyr Leu Pro Ser Tyr Glu Arg Val Pro His Leu Pro His Pro Trp Ala  
355 360 365

Leu Cys Ala Pro  
370

<210> 130

<211> 256

<212> PRT

<213> Homo sapien

<400> 130

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

138

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60

Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80

Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
85 90 95

Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
100 105 110

Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu  
115 120 125

Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser  
130 135 140

Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg  
145 150 155 160

Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser  
165 170 175

His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr  
180 185 190

Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser  
195 200 205

Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe  
210 215 220

Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp  
225 230 235 240

Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met  
245 250 255

139

&lt;211&gt; 492

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 131

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

140

Ser	His	His	Ser	Asp	Thr	Pro	Thr	Thr	Leu	Ala	Ser	His	Ser	Thr	Lys
225				230					235						240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
 275                    280                    285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
 305                   310                   315                   320

Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe  
325 330 335

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
340 345 350

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
355 360 365

Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly  
370 375 380

Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val  
385 390 395 400

Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg  
405 410 415

Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr  
420 425 430

His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val  
435 440

Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Arg Leu Gly  
450 455 460

141

Pro Thr Gly Gln Gly Lys Gln Arg Val Trp Leu Gly Lys Asp Ser Glu  
465                   470                   475                   480

Gly Gly Thr Trp Lys Thr Gln Arg Ala Trp Lys Arg  
485                   490

<210> 132  
<211> 483  
<212> PRT  
<213> Homo sapien

<400> 132

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1                   5                   10                   15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20                   25                   30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35                   40                   45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50                   55                   60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65                   70                   75                   80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85                   90                   95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100                105                110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115                120                125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130                135                140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145                150                155                160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165                170                175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180                185                190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe  
325 330 335

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
340 345 350

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
355 360 365

Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly  
370 375 380

Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val  
385 390 395 400

Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg  
405 410 415

Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr  
420 425 430

143

His Pro Met Ser Glu Trp Arg Val Tyr Glu Glu Lys Lys Lys Glu Val  
435 440 445

Pro Ala Val Pro Glu Thr Leu Lys Lys Lys Arg Arg Asn Phe Ala Glu  
450 455 460

Leu Lys Ile Lys Arg Leu Arg Lys Lys Phe Ala Lys Arg Cys Phe Glu  
465 470 475 480

Arg Gln Gly

<210> 133

<211> 150

<212> PRT

<213> Homo sapien

<400> 133

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp  
50 55 60

Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Ala Val Cys Gln  
65 70 75 80

Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp  
85 90 95

Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg  
100 105 110

Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser  
115 120 125

Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala  
130 135 140

Ala Thr Ser Ala Asn Leu

144

145

150

<210> 134  
<211> 168  
<212> PRT  
<213> Homo sapien

&lt;400&gt; 134

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Leu Ser Thr Gly Val Ser Phe Phe Leu Ser  
50 55 60

Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser  
65 70 75 80

Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Ala Val  
85 90 95

Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala  
100 105 110

Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His  
115 120 125

Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys  
130 135 140

Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala  
145 150 155 160

Val Ala Ala Thr Ser Ala Asn Leu  
165

<210> 135  
<211> 79  
<212> PRT  
<213> Homo sapien

&lt;400&gt; 135

145

Ser Pro Glu Trp Leu Thr Leu Ile Ser Ser Pro Gly Lys Asn Tyr Gly  
1 5 10 15

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu  
20 25 30

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr  
35 40 45

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser  
50 55 60

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
65 70 75

<210> 136  
<211> 398  
<212> PRT  
<213> Homo sapien

<400> 136

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe  
325 330 335

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
340 345 350

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
355 360 365

Ser Ala Glu Val Pro Phe His Ile Met Leu Thr Asn Met Gly Thr Met  
370 375 380

Glu Tyr His Asn Val Gly Ala Ile Arg Phe Arg His Asn Tyr  
385 390 395

<210> 137  
<211> 36  
<212> PRT  
<213> Homo sapien  
  
<400> 137

Gly Arg Leu Leu Leu Leu Leu Glu Phe Lys Leu Leu Thr Met Tyr  
1 5 10 15

Gly Leu Met Pro Gly Lys Cys Cys Gly Gly Ser Gln Glu Asp Trp  
20 25 30

Pro Arg Glu Pro  
35

<210> 138  
<211> 264  
<212> PRT  
<213> Homo sapien  
  
<400> 138

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Phe Asn  
50 55 60

Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg  
65 70 75 80

Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu  
85 90 95

Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Gln Leu  
100 105 110

Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr  
115 120 125

Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr  
130 135 140

Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln  
145 150 155 160

Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val  
165 170 175

Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val  
180 185 190

Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala  
195 200 205

Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His  
210 215 220

Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys  
225 230 235 240

Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala  
245 250 255

Val Ala Ala Thr Ser Ala Asn Leu  
260

<210> 139  
<211> 241  
<212> PRT  
<213> Homo sapien

<400> 139

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Phe Leu  
50 55 60

149

Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe  
65 70 75 80

Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly  
85 90 95

Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr  
100 105 110

Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser  
115 120 125

Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly  
130 135 140

Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala  
145 150 155 160

Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn  
165 170 175

Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met  
180 185 190

Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser  
195 200 205

Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly  
210 215 220

Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn  
225 230 235 240

Leu

<210> 140  
<211> 92  
<212> PRT  
<213> Homo sapien

<400> 140

Met Ala Cys His Asn Leu Leu Ser Pro Gln Ala Val Cys Gln Cys Arg  
1 5 10 15

Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr  
20 25 30

150

His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val  
35 40 45

Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Arg Leu Gly  
50 55 60

Pro Thr Gly Gln Gly Lys Gln Arg Val Trp Leu Gly Lys Asp Ser Glu  
65 70 75 80

Gly Gly Thr Trp Lys Thr Gln Arg Ala Trp Lys Arg  
85 90

<210> 141

<211> 420

<212> PRT

<213> Homo sapien

<400> 141

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
1 5 10 15

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
20 25 30

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
35 40 45

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
50 55 60

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
65 70 75 80

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
85 90 95

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
100 105 110

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
115 120 125

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
130 135 140

151

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
145 150 155 160

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
165 170 175

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
180 185 ~190

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
195 200 205

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
210 215 220

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
225 230 235 240

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
245 250 255

Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe  
260 265 270

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
275 280 285

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
290 295 300

Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly  
305 310 315 320

Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val  
325 330 335

Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg  
340 345 350

Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr  
355 360 365

His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val  
370 375 380

Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly

152

385

390

395

400

Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr  
405 410 415

Ser Ala Asn Leu  
420

<210> 142  
<211> 485  
<212> PRT  
<213> Homo sapien

<400> 142

Met Pro Gln Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu  
1 5 10 15

Thr Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr  
20 25 30

Gly Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser  
35 40 45

Ala Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val  
50 55 60

Ser Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser  
65 70 75 80

Ser Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro  
85 90 95

Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro  
100 105 110

Val Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val  
115 120 125

Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro  
130 135 140

Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser  
145 150 155 160

Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro  
165 170 175

Ala Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser  
180 185 190

Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser  
195 200 205

Ala Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile  
210 215 220

Pro Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr  
225 230 235 240

Lys Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr  
245 250 255

Ser Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe  
260 265 270

Phe Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu  
275 280 285

Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser  
290 295 300

Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser  
305 310 315 320

Asn Ile Lys Phe Arg Pro Gly Ser Val Val Gln Leu Thr Leu Ala  
325 330 335

Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn  
340 345 350

Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp  
355 360 365

Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala  
370 375 380

Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu  
385 390 395 400

Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys  
405 410 415

154

Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr  
420 425 430

Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr  
435 440 445

Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala  
450 455 460

Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala  
465 470 475 480

Thr Ser Ala Asn Leu  
485

<210> 143

<211> 255

<212> PRT

<213> Homo sapien

<400> 143

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp  
50 55 60

Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile  
65 70 75 80

Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro  
85 90 95

Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile  
100 105 110

Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala  
115 120 125

Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val  
130 135 140

Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly  
145 150 155 160

Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val  
165 170 175

Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly  
180 185 190

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu  
195 200 205

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr  
210 215 220

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser  
225 230 235 240

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
245 250 255

<210> 144

<211> 517

<212> PRT

<213> Homo sapien

<400> 144

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

156

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Val Ser Ile Gly Leu Ser Phe Pro Ser Ser Pro Glu Ala Ala Ile  
305 310 315 320

Arg Thr Val His Thr Leu Cys Ile Lys Pro Glu Ser Phe Pro Ser His  
325 330 335

Pro Ser Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser

157

340

345

350

Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala  
355 360 365

Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn  
370 375 380

Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp  
385 390 395 400

Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala  
405 410 415

Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu  
420 425 430

Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys  
435 440 445

Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr  
450 455 460

Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr  
465 470 475 480

Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala  
485 490 495

Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala  
500 505 510

Thr Ser Ala Asn Leu  
515

<210> 145

<211> 180

<212> PRT

<213> Homo sapien

<400> 145

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
1 5 10 15

Ile Lys Phe Arg Pro Gly Ser Val Val Gln Leu Thr Leu Ala Phe  
20 25 30

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
35 40 45

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
50 55 60

Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly  
65 70 75 80

Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val  
85 90 95

Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg  
100 105 110

Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr  
115 120 125

His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val  
130 135 140

Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly  
145 150 155 160

Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr  
165 170 175

Ser Ala Asn Leu  
180

<210> 146  
<211> 232  
<212> PRT  
<213> Homo sapien

<400> 146

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu

159

50

55

60

Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu  
65 70 75 80

Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr  
85 90 95

Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr  
100 105 110

Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln  
115 120 125

Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val  
130 135 140

Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val  
145 150 155 160

Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala  
165 170 175

Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His  
180 185 190

Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys  
195 200 205

Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala  
210 215 220

Val Ala Ala Thr Ser Ala Asn Leu  
225 230

<210> 147

<211> 396

<212> PRT

<213> Homo sapien

<400> 147

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

160

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

161

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe  
325 330 335

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
340 345 350

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
355 360 365

Ser Gly Glu Ala Thr Ser Leu Ala Ala Gln His His Ala Gly Ala  
370 375 380

Pro Leu Leu Pro Val Ser Gly Ser Pro Leu Phe Pro  
385 390 395

<210> 148

<211> 325

<212> PRT

<213> Homo sapien

<400> 148

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

162

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Ser Glu  
325

&lt;210&gt; 149

&lt;211&gt; 409

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 149

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro

164

210

215

220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Arg Pro Gly Ser Val Val Gln Leu Thr Leu Ala Phe  
325 330 335

Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln  
340 345 350

Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val  
355 360 365

Ser Gly Cys Leu Ser Val Pro Pro Lys Glu Leu Arg Ala Ala Gly His  
370 375 380

Leu Ser Ser Pro Gly Tyr Leu Pro Ser Tyr Glu Arg Val Pro His Leu  
385 390 395 400

Pro His Pro Trp Ala Leu Cys Ala Pro  
405

<210> 150  
<211> 379  
<212> PRT  
<213> Homo sapien

<400> 150

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

165

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50 55 60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65 70 75 80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85 90 95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100 105 110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115 120 125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130 135 140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145 150 155 160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165 170 175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180 185 190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195 200 205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210 215 220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225 230 235 240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245 250 255

166

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260 265 270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275 280 285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile  
305 310 315 320

Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr  
325 330 335

His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro  
340 345 350

Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr  
355 360 365

Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
370 375

<210> 151  
<211> 110  
<212> PRT  
<213> Homo sapien

<400> 151

Val Val Thr Trp His Asn Pro Gly Ala Gly Val Pro Gly Trp Gly Ile  
1 5 10 15

Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr  
20 25 30

Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln  
35 40 45

Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr  
50 55 60

Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp  
65 70 75 80

Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu  
85 90 95

Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
100 105 110

<210> 152  
<211> 127  
<212> PRT  
<213> Homo sapien

<400> 152

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly  
50 55 60

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu  
65 70 75 80

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr  
85 90 95

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser  
100 105 110

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
115 120 125

<210> 153  
<211> 336  
<212> PRT  
<213> Homo sapien

<400> 153

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala

168

35

40

45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Val Ser  
50                       55                       60

Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly Ser Ser  
65                       70                       75                       80

Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu Pro Ala  
85                       90                       95

Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val Pro Val  
100                      105                       110

Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp Val Thr  
115                      120                       125

Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
130                      135                       140

His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr  
145                      150                       155                       160

Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala  
165                      170                       175

Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly  
180                      185                       190

Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala  
195                      200                       205

Arg Ala Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro  
210                      215                       220

Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys  
225                      230                       235                       240

Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser  
245                      250                       255

Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe  
260                      265                       270

Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu  
275                      280                       285

Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu  
290 295 300

Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn  
305 310 315 320

Ile Lys Phe Ser Gln Glu Leu Trp Trp Gln Asn Lys Arg Ser Ser Asn  
325 330 335

<210> 154  
<211> 55  
<212> PRT  
<213> Homo sapien

<400> 154

Met Ala Thr Gln Leu Ile Leu Val Gln Met Ser Leu Phe Pro Asp Ala  
1 5 10 15

Pro His Asp Pro Ser Ser Leu Gly Gly Met His Pro Ser Ser Val Ser  
20 25 30

His Phe Arg Ala Phe Cys Thr Leu Leu Thr Leu Ser Arg Ile Pro Ala  
35 40 45

Ile Trp Val Gln Ala Ser Gln  
50 55

<210> 155  
<211> 97  
<212> PRT  
<213> Homo sapien

<400> 155

Met Asn His Leu Arg His Phe Cys Ile Thr Glu Asp Leu Ala Leu Pro  
1 5 10 15

Ala Val Leu Gly Met Leu Arg Val Gln Ala Glu Ala Arg Glu Ala Gly  
20 25 30

Leu Arg Gly Gln Lys Gln Gly Leu Gly Gln Ala Ser Pro Asp Arg Glu  
35 40 45

Glu Gly Leu Arg Ser Lys Pro Ala Val Leu Leu Ala Gly Gly Pro Gly  
50 55 60

Gly Tyr Lys Leu Leu Cys Ala Leu His Lys Pro Glu Ser Pro Thr Arg

170

65	70	75	80
----	----	----	----

Glu Asp Val Cys Glu Glu Pro Glu Thr Leu Asn Pro Ile Lys Arg Glu  
85 90 95

Lys

<210>	156
<211>	52
<212>	PRT
<213>	Homo sapien

<400> 156

Met Leu Cys Ala Ile Ser Ile Ser Leu Val Ile Phe Phe Asn Lys His  
1 5 10 15

Glu Ser Ile Lys Lys Lys Arg Arg Lys Lys Lys Ala Gly Gly Thr Leu  
20 25 30

Gly Gln Ser Gly Pro Gly Asp Trp Phe Pro Ala Asn Ser Thr Ile  
35 40 45

Ser Arg Thr Arg  
50

```
<210> 157
<211> 23
<212> DNA
<213> Artificial sequence
```

<220>  
<223> Synthetic

<400> 157  
cacttccttt aqttttqccc tqg

23

```
<210> 158
<211> 23
<212> DNA
<213> Artificial sequence
```

<220>  
<223> Synthetic

<400> 158  
atcctqaatt ctqaqaccat cca

23

<210> 159  
<211> 21  
<212> DNA

171

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;400&gt; 159

gcctccagca cactcttcag t

21

&lt;210&gt; 160

&lt;211&gt; 25

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;400&gt; 160

agccggagga gatgtggctc taccg

25

&lt;210&gt; 161

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;400&gt; 161

ccgcttccca gagactcatc

20

&lt;210&gt; 162

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;400&gt; 162

gcacaaaacat cggcttggt

19

&lt;210&gt; 163

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;400&gt; 163

agagagacat ttctgaaatg gctgtct

27

&lt;210&gt; 164

&lt;211&gt; 21

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

<220>  
<223> Synthetic  
  
<400> 164  
cccagcacccg actactacca a

21

<210> 165  
<211> 20  
<212> DNA  
<213> Artificial sequence

<220>  
<223> Synthetic  
  
<400> 165  
agctgccccgt agttctttcg

20

<210> 166  
<211> 27  
<212> DNA  
<213> Artificial sequence

<220>  
<223> Synthetic  
  
<400> 166  
ctgaaaggcag gtcacccctg agatcct

27

<210> 167  
<211> 21  
<212> DNA  
<213> Artificial sequence

<220>  
<223> Synthetic  
  
<400> 167  
cagagcttgg ccaggttcta a

21

<210> 168  
<211> 19  
<212> DNA  
<213> Artificial sequence

<220>  
<223> Synthetic  
  
<400> 168  
tgcttagggtg cccctctgt

19

<210> 169  
<211> 24  
<212> DNA  
<213> Artificial sequence

173

<220>  
<223> Synthetic

<400> 169  
ccttagggc ctgggacaaac cacg

24

<210> 170  
<211> 22  
<212> DNA  
<213> Artificial sequence

<220>  
<223> Synthetic

<400> 170  
tggataacaa gcccacaaat ga

22

<210> 171  
<211> 23  
<212> DNA  
<213> Artificial sequence

<220>  
<223> Synthetic

<400> 171  
cctctagttc cagccccttt tag

23

THIS PAGE BLANK (USPTO)